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### Images of healthy aging

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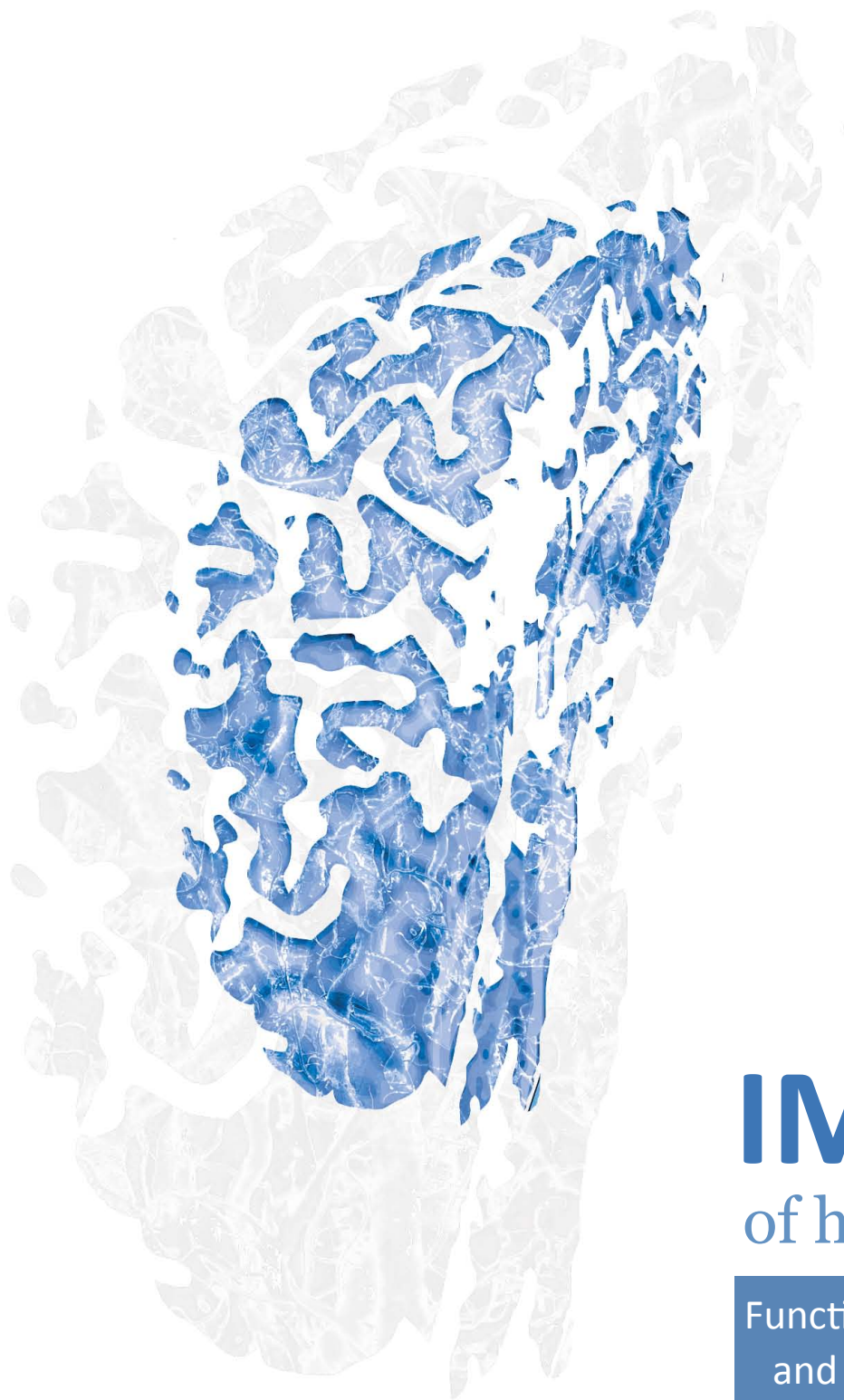
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# IMAGES

of healthy aging

Functional brain networks  
and selective attention

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 functional brain networks and selective attention**

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# Chapter 1

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General introduction

# 1 General introduction

Growing old is not just the passive effect of the passage of time, but it is an active adaptive process in which there is an interplay between increased experience and knowledge and the physical declines that are associated with aging. Aging equals change. While some cognitive abilities decrease with age, others improve or are not affected by aging. On the bright side, older adults often experience higher affective well-being and are more skilled at emotion regulation than their younger counterparts (Carstensen & Mikels, 2005; Scheibe & Carstensen, 2010). Moreover, increased life experience is associated with improved and more flexible problem solving in daily life (Blanchard-Fields, 2007) as well as improved reasoning about social conflicts due to the ability to take another's perspective, the ability to compromise and the ability to recognize the limits of one's own knowledge (Grossmann et al., 2010). On the downside, aging is associated with a decline in a wide range of (complex) cognitive functions (for reviews see: Grady, 2012; Park & Reuter-Lorenz, 2009), such as selective attention and working memory.

Due to an increasing life-span, more and more people reach old age. For this large group of older adults, preservation of cognitive functioning is very important. A decline in cognitive functioning is directly related to a decline in the experienced well-being of older adults (Wilson et al., 2013). In addition, age-related declines in cognitive functioning can impose high socio-economic costs, related to early retirement and health care. An important goal of the studies described in this thesis was to identify the neural mechanisms that underlie age-related declines in cognitive functioning. One of the approaches we used was to consider individual differences. Age-related changes in cognitive functioning are highly variable between individuals. Some older adults are able to maintain high levels of cognitive functioning into old age, while others show a much more rapid decline. Even in very basic reaction time tasks, inter-individual variability is larger in old than in younger participants (Hultsch et al., 2002). By linking the individual differences in cognitive functioning to individual differences in underlying mechanisms, we can increase our understanding of the origins of the age-related decline in cognitive functioning. Identifying the brain mechanisms that enable some older adults to maintain high levels of cognitive performance, is a first step towards development of interventions that allow other older adults to improve cognitive functioning. Although aging equals change, affecting functioning in both positive and negative ways, in this thesis we focus on the mechanisms behind the age-related decline in different cognitive functions.

## 1.1 Theories of cognitive aging

There has been ample research on the nature of the cognitive changes that accompany aging. Based on this research, a number of influential theories have been proposed about

cognitive aging. Salthouse (1996) posited that the cognitive decline associated with aging can be explained by a general reduction in processing speed. He suggested that when processing is slowed, especially the execution of complex cognitive processes, consisting of multiple processing stages, will decline. Salthouse demonstrated that slowing of information processing can indeed account for a large proportion of the age-related variance across a variety of cognitive tasks (Salthouse, 1991; Salthouse, 1996). However, general slowing cannot fully account for the age-related changes occurring in cognitive functions such as memory or cognitive control (Bugg et al., 2007; Park et al., 1996; Span et al., 2004).

Other researchers have suggested that deficits in suppressing irrelevant information (inhibitory deficits) are the driving factor behind age-related changes in cognitive functioning. Hasher and Zacks (1988) proposed the inhibitory deficit theory, in which they pose that there is an age-related deficit in inhibitory functions (selective attention), that normally constrain the contents of working memory. As the ability to filter information declines, this also affects other processes besides working memory, such as response suppression and task switching. In another theoretical framework, it has been suggested that the reduced capacity of working memory itself is an important factor influencing age-related declines in other domains (Park et al., 2002; Park et al., 1996). The active manipulation of information in mind requires working memory capacity. Therefore, reduced working memory capacity can also indirectly affect other functions, such as decision making.

These general theories of cognitive aging suggest that age-related declines in functioning are mainly due to decline in a single function. However, such a unitary mechanism of age-related decline is not very likely, considering that the rate of decline in different cognitive functions typically varies between people. For example, some older adults have excellent episodic memory function but impaired cognitive control functions, and vice versa (Glisky et al., 1995; Park et al., 1996). Therefore, the effects of aging on cognitive functioning should probably be perceived as a complex interplay of changes in multiple cognitive functions with varying rates. In addition, the effects of cognitive decline in some domains can be mitigated by the large amount of knowledge and experience that older adults have acquired over the life span (Park & Reuter-Lorenz, 2009).

## 1.2 Age-related changes in brain structure

To understand the age-related changes in cognitive functioning, it is important to understand the neural mechanisms underlying these changes. The most obvious effect of aging is the widespread deterioration in the structural anatomy of the brain. Reduced white matter is generally observed in frontal areas of the aging brain, whereas

gray matter reductions are mainly found in frontal and parietal cortices, as well as in the insula and hippocampus (Good et al., 2001; Gunning-Dixon et al., 2009; Madden et al., 2009; Raz et al., 2005; Resnick et al., 2003). These structural changes have been related to age-related decline in cognitive function. In a study by Persson and colleagues (2006) for example, a decline in episodic memory was related to both a decline in hippocampal gray matter volume and a decrease in fractional anisotropy, a measure of white matter integrity, in the anterior corpus callosum. Decreased fractional anisotropy in anterior tracts has also been related to poorer performance in cognitive control tasks, while lower fractional anisotropy in posterior tracts was associated with decreased visual memory (Davis et al., 2009). Although the structural integrity of the brain is crucial for cognitive functioning, the number of studies that have established direct links between cognition and structural changes in the aging brain is limited (see review, Tisserand & Jolles, 2003) and inconsistent results have been reported (e.g. Salami et al., 2012). Therefore, it is not enough to understand the effect of aging on brain structure. To find a more direct link between age-related effects on brain and behavior, brain function needs to be studied as well.

### 1.3 Age-related changes in brain function

Age-related changes in brain function can be studied by examining differences in brain activity between older and younger adults in different conditions. While performing the same cognitive task, older adults tend to show increased (bilateral) activation in comparison to younger participants, mainly in frontal brain regions (e.g. Cabeza et al., 1997; Cabeza, 2002; Gutchess et al., 2005; Madden et al., 1999; Reuter-Lorenz et al., 2000; Vallesi et al., 2011). In addition, activation in more posterior brain regions is often declined in older compared to younger participants (Davis et al., 2008). Although this pattern of findings is rather reliable, it has provoked extensive discussion in the literature.

In addition to the different theories on cognitive aging, describe above, three different theoretical frameworks have been put forward to explain the age-related increases in brain activation (Grady, 2012). The dedifferentiation theory suggests that the enhanced activation of brain areas in older adults might be due to a decrease in functional distinction between brain areas (Baltes & Lindenberger, 1997; Carp et al., 2011a; Dennis & Cabeza, 2011; Park et al., 2004). For example, distinct categories of visual stimuli activate areas in the visual cortex of older adults less selectively than in young (Park et al., 2004). A related framework explains age-related effects in terms of less efficient use of neural resources. This theory suggests that increased activation in older adults signals that they are no longer able to selectively engage brain regions that are required for task performance (Morcom et al., 2007; Rypma et al., 2007; Stevens et al., 2008). This supposedly happens because older adults are unable to resolve the competition among brain regions that could potentially be useful for task performance (Logan et al., 2002). It is important to

note that both of these frameworks portray aging as a process of passive decline. In contrast, the compensation theory emphasizes flexibility of the aging brain. This theory suggests that increases in task related activation in older adults reflect engagement of additional brain areas to maintain task performance at an adequate level despite impaired function elsewhere in the brain (Cabeza, 2002; Davis et al., 2008; Park & Reuter-Lorenz, 2009). Research in which higher levels of activation have been found to be associated with increased levels of performance have generally been interpreted as evidence for compensation whereas negative associations of brain activation with performance have been attributed to dedifferentiation or to less efficient use of neural resources. Because there is substantial evidence supporting each of these alternative theoretical frameworks, most researchers now take the perspective that all three mechanisms (dedifferentiation, less efficient use of neural resources and compensation) may play a role in aging and that they are not mutually exclusive.

#### 1.4 Selective attention in the brain

In this thesis, our goal was to extend knowledge on the way in which brain function and behaviour are linked in older adults. To this end, we studied one of the core cognitive functions that is required for adequate functioning in daily life, and that is found to be particularly affected by aging; selective attention. Selective attention enables the selection of relevant information from the environment, while ignoring irrelevant information. Most of the time, we do not realize that large amounts of information are coming in through our senses. It has been estimated that the human retina can send around 10 million bits of information to the brain every second (Koch et al., 2006). We do not experience an information overload, because our brain very efficiently filters out only the information that is relevant to us at any given moment. However, this ability to selectively attend to relevant information declines with aging, and may affect the ability of older adults to function efficiently in various situations. For example, when you are talking to a friend on the phone, the background noise of a television can be very distracting. In a more dangerous situation, such as driving a car in crowded traffic, being distracted by a billboard on the side of the road can have grave consequences for both the driver and other people on the road. In addition to these direct effects, reduced selective attention indirectly affects other cognitive functions such as memory and decision making (Gazzaley et al., 2005a; Hasher & Zacks, 1988).

It has been found that there are two separate mechanisms that underlie selective attention; suppression of irrelevant information and enhancement of relevant information (Gazzaley et al., 2005a; Hillyard et al., 1998). Two brain areas have been suggested to play an important role in both suppression and enhancement of information; the frontal eye fields (FEF) and the superior parietal lobule (SPL). These brain areas influence the baseline firing rates of neurons and neural synchronization in the sensory cortices (Corbetta &



Shulman, 2002; Desimone & Duncan, 1995; Kastner & Ungerleider, 2000; Reynolds & Chelazzi, 2004). This leads to an increase in the neural responsiveness in the sensory cortices when a stimulus is attended. As a result, people are able to detect a stimulus better and faster when it is presented at an attended location or when it contains other attended features whereas unattended stimuli. For unattended stimuli the opposite pattern emerges; neural responsiveness is reduced leading to decreased stimulus detection.

There are strong indications that these two selective attention mechanisms are affected differentially by age. Suppression of irrelevant information declines with age, while enhancement of relevant information remains intact (de Fockert et al., 2009; Gazzaley et al., 2005a; Gazzaley et al., 2008; Haring et al., 2013; Mager et al., 2007). This dissociation is nicely illustrated in a study by Gazzaley and colleagues (2005a). In this study, older and younger participants performed a working memory task in which they were presented with relevant (to be remembered) and irrelevant images. Additionally, there was a passive view condition, in which participants were instructed to view the pictures without attempting to remember them. In both age groups, brain activation was found to be increased for relevant images compared to passive view, while only younger participants showed reduced activation for irrelevant images compared to the passive view condition. It should be noted that the effects of aging on the enhancement of relevant information is still a topic of debate, as other studies have shown a deficit in older adults in the enhancement of relevant information when it is accompanied by distractor stimuli (Chee et al., 2006; Quigley et al., 2010; Schmitz et al., 2010). Currently, only little is known about the mechanisms that underlie this age-related decline in selective attention. One of the goals of this thesis (see chapters 5-7) was to gain knowledge about these mechanisms, specifically by focusing on the neural underpinnings of individual differences in selective attention in young and older adults.

When studying the brain mechanisms underlying individual differences in selective attention, the integration of information (connectivity) between distant brain areas should be studied in addition to activation in individual brain areas. Selective attention is implemented by connectivity from the FEF and SPL to the sensory cortices. In addition, the SPL and FEF need to work together to achieve a common goal, which also requires extensive integration of information. Chica and colleagues (2013), for example, demonstrated that the integration of information between the FEF and SPL is indeed an important aspect of selective attention. They showed that increased connectivity between these areas was associated with improved detection of target stimuli at attended locations. Together, the bilateral FEF and SPL have been referred to as the dorsal attention network (DAN, Fox et al., 2005; Toro et al., 2008). In this thesis we especially focused on the relation between connectivity and selective attention and how this is modulated by age.

## 1.5 Age-related changes in functional connectivity

Functional connectivity, that is the association between activity in different brain regions, is not only important for selective attention but also for effective cognitive functioning in general (Biswal et al., 2010; Kelly et al., 2008; Spreng & Schacter, 2011; Wen et al., 2012). Therefore, it is likely that changes in connectivity are an important factor in age-related changes in cognitive functioning. There are indeed strong indications that functional connectivity is affected by aging (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008). One specific functional network, the default mode network (DMN) has received a lot of attention in the aging literature. The DMN is a network of brain areas that is more active while participants are not engaging in a specific task (i.e. in a resting state) than during task performance (Buckner et al., 2008; Greicius et al., 2003; Raichle et al., 2001). One consistent finding, in both task and resting state studies, is that connectivity within the DMN significantly decreases with advancing age (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Grady et al., 2010; Sambataro et al., 2010). Highly relevant is that older adults with a larger decrease in connectivity within the DMN, tend to perform worse in processing speed and working memory tasks (Andrews-Hanna et al., 2007; Sambataro et al., 2010).

There are indications that age-related changes in functional connectivity are not limited to the DMN. The fronto-parietal control network (FPCN) is a network that is involved in cognitive control and maintenance of task goals or task sets in working memory (Braver et al., 2009; Spreng et al., 2013; Spreng et al., 2010; Vincent et al., 2008). Rieckmann and colleagues (2011) showed that connectivity within the FPCN was reduced in older adults during a working memory task. Moreover, connectivity was found to be reduced with aging in the DAN and the motor network, as well (Andrews-Hanna et al., 2007; Wu et al., 2007).

The studies mentioned above have demonstrated the importance of studying the role of connectivity changes in cognitive aging. However, these studies examined only a small part of the age-related changes in functional connectivity; examinations were limited to pre-specified networks. Moreover, most studies so far, were constrained to connectivity within networks, while connectivity between different functional networks has received hardly any attention. Efficient functioning requires integration of information within and between different functional networks. Therefore, another important goal of this thesis (chapters 2-4) was to study the functional changes in the aging brain in a more comprehensive fashion, by examining not only connectivity within different functional brain networks, but also between functional networks.

### 1.6 Methods to study age-related effects on brain function

To study neural mechanisms underlying the effects of aging on selective attention as well as effects of aging on functional connectivity we have used electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). EEG is the recording of electrical activity from the scalp. EEG measures voltage fluctuations resulting from ionic current flows within large assemblies of neurons in the brain. A unique feature of EEG is that fluctuations in brain activity can be measured at the millisecond scale. This high temporal resolution enables specification of the stages of stimulus processing in which age-related differences might occur. However, because the EEG signal reflects the summed contribution from many different sources in the brain, the spatial resolution of EEG is low. The EEG signal is generally subdivided into three categories of constituting signals (Tallon-Baudry & Bertrand, 1999). The spontaneous background activity is always present and unrelated to the experimental condition. Induced activity is activity that is elicited by the experimental condition, however it is not phase locked to the onset of the stimulus. In contrast, evoked activity is activity that is precisely phase locked to the onset of the stimulus.

Traditionally, studies have focused on evoked activity in the EEG signal. By stimulus- or response-locked averaging over different occurrences of a stimulus, an average pattern of evoked activity can be obtained. This is called an evoked or event related potential (ERP, Luck & Ford, 1998). The ERP consist of different peaks, or components, which are typically related to specific stages of processing or functions. This important characteristic of the ERP was utilized in chapter 5 in this thesis, where we investigated in which stage of processing age-related impairment in suppression of irrelevant information arises.

Recently, the interest of many researchers has shifted to the oscillatory changes that reflect induced activity. One reason is that researchers have realized that oscillatory changes are an important mechanism for inter-neuronal communication and for the binding of information that is processed in distributed brain areas (Roach & Mathalon, 2008). The tool that is most often used to study oscillatory changes in brain activity is time-frequency analysis. Time-frequency analyses can be used to examine stimulus induced changes in oscillatory power. This method was used in chapters 5 and 6 to assess how differences in oscillatory power, both before and after stimulus onset, are related to perception and attention. By investigating synchronous changes in the power or the phase of oscillatory activity at different electrode sites, it is possible to study connectivity. In chapter 5, we have used this method to study how integration of information in different brain areas is related to the ability to suppress the processing of irrelevant information in young and older adults.

A tool that compliments the results obtained from EEG analysis in many ways is fMRI (Logothetis et al., 2001; Ogawa et al., 1990). Whereas EEG directly records the electrical

signal generated in the brain, fMRI is an indirect measure of brain activity. The fMRI technique uses a strong magnetic field to record the changes in the magnetic properties of the blood that are induced by changes in brain activity. More specifically, when a brain area becomes more active, there is a local increase in oxygen rich blood that is greater than the amount of oxygen that can be used by the brain tissue. This is called the hemodynamic response. This response results in a local increase of the proportion of oxygenated versus deoxygenated blood. The difference in magnetic properties of deoxygenated and oxygenated blood enables the detection of local increases in brain activity. The hemodynamic response develops slowly, over the course of 6 to 8 seconds. Therefore the temporal resolution of fMRI is limited to the range of seconds. The spatial resolution of fMRI depends on the strength of the magnetic field that is used. Using a scanner of 3 Tesla, which is a common field strength for neuroscientific studies, the resolution is in the order of a few millimeters.

fMRI data has traditionally been analyzed by comparing brain activity between different task conditions. This has allowed researchers to disentangle the function of specific brain areas. In chapter 7, we have used this technique to find which brain areas are involved in perceiving and responding to target stimuli in younger and older adults. fMRI data can also be used to investigate connectivity between brain areas. To this end, different analysis methods are available that each have their unique advantages and disadvantages. These analysis methods complement each other in the information they can provide and therefore, we have used different methods in the different chapters of this thesis. Seed based connectivity (Biswal et al., 1995; Fox et al., 2005), uses one or more brain areas as seed regions and investigates how these brain areas are functionally connected to other parts of the brain (see chapters 2 and 7). Independent component analysis (van de Ven et al., 2004) instead uses a data-driven approach to identify a set of maximally independent functional networks in the brain (see chapter 4). Graph theory (Rubinov & Sporns, 2010) captures the properties of the entire connectivity pattern of a large set of brain regions in a relatively small number of complex network measures (see chapters 3 and 4). In the different chapters, we illustrated how these different methods all contribute to our understanding of the way brain areas communicate and how this is affected by aging.

## 1.7 Outline of the chapters

The overall aim of the first part of this thesis was to increase the knowledge on the effects of aging on functional connectivity, within and between functional brain networks. Most aging studies thus far focused on functional connectivity in one or a limited number of pre-specified networks. With the study described in chapter 2, we aimed to investigate whether connectivity changes are restricted to specific functional networks and whether connections between functional networks are affected by aging, as well.

We used a combination of seed-based connectivity and cluster analyses to examine age-related connectivity changes within and between five different brain networks. The results showed that aging is associated with both decreases in specific within-network connectivity and increases in between-network connectivity.

In chapter 3, these functional connectivity changes were analyzed in more detail. To this end we used graph theory, a method often used in the analysis of social networks, to provide more information about the effects of aging on the efficiency of communication within and between different networks. In addition, on account of the results in chapter 2, we investigated to what extent separable functional networks could still be identified in older participants. We showed that efficiency of connectivity is decreased in older compared to younger participants and that functional networks become less separable in old age.

Given these changes in the organization of functional networks described in chapters 2 and 3, we examined in chapter 4 whether these functional connections are still flexible in older adults. Are older adults still able to adapt functional connectivity to the demands of the task at hand? In this study we combined Independent Component Analysis (ICA) and graph theory to answer this question. The results demonstrated that connectivity remains flexible in older adults. However, we observed clear differences in the factors that drive connectivity changes in old compared to young adults.

The aim of the second part of this thesis was to study the neural mechanisms that underlie changes in selective attention in older adults. In chapter 5, we used combination of ERP and time-frequency analysis, thereby considering both power and connectivity measures, to get a more in-depth picture of the factors that were related to individual differences in suppression of irrelevant information. The results demonstrated a decline in suppression of irrelevant information in early perceptual stages of processing in a subgroup of older adults. The analysis of the pre-stimulus brain state showed that preparation, through top-down control prior to stimulus onset, is an important factor to limit the interference from irrelevant information.

In chapter 6, we investigated the nature and the extent of these effects of pre-stimulus brain states on subsequent processing. Participants performed a task in which two stimuli were presented in rapid succession. These stimuli were sometimes perceived as one integrated percept and sometimes as two separate stimuli. Time-frequency analyses revealed that the brain state prior to stimulus was strongly related to how that stimulus was perceived.

The study described in chapter 7 explicitly focused on why suppression of irrelevant information but not enhancement of relevant information is affected by aging. This dissociation is especially striking because top-down suppression and enhancement

are thought to originate from the same fronto-parietal network. In this study we used fMRI to investigate the responses to relevant target and salient irrelevant stimuli. Age-related differences in the underlying selective attention mechanisms were studied using a combination of blood-oxygen level dependent (BOLD) activation and seed-based connectivity measures. The results demonstrated that older adults recruit additional brain areas during detection of target stimuli, whereas no additional brain areas were recruited when they suppressed the processing of irrelevant target stimuli. The additional recruitment during target detection was related to more accurate detection of target stimuli, suggesting that this reflects a compensation mechanism.

In chapter 8, the different findings of the studies described in this thesis are integrated. In addition, critical considerations are presented along with perspectives for future research.



# Chapter 2

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## Functional connectivity in the aging brain during task performance

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## 2 Functional connectivity in the aging brain during task performance

### 2.1 Abstract

The importance of studying connectivity in the aging brain is increasingly recognized. Recent studies have shown that connectivity within the default mode network is reduced with age and have demonstrated a clear relation of these changes with cognitive functioning. However, research on age related changes in other functional networks is sparse and mainly focused on pre-specified functional networks. Using functional magnetic resonance imaging, we investigated age related changes in functional connectivity during a visual oddball task in a range of functional networks. It was found that compared to young participants, elderly showed a decrease in connectivity between areas belonging to the same functional network. This was found in the default mode network and the somatomotor network. Moreover, in all identified networks, elderly showed increased connectivity between areas within these networks and areas belonging to different functional networks. Decreased connectivity within functional networks was related to poorer cognitive functioning in elderly. The results were interpreted as a decrease in the specificity of functional networks in older participants.

### 2.2 Introduction

Recent research has shown that connectivity between brain areas is crucial for effective cognitive functioning (Biswal et al., 2010; Kelly et al., 2008; Spreng & Schacter, 2011; Wen et al., 2012). At the same time, it is becoming clear that aging affects connectivity in the brain on a large scale (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008). Therefore, changes in connectivity might be an important factor underlying the level of cognitive decline a person will experience with advancing age. Research on connectivity in the brain has identified a number of functional networks; groups of brain areas that show a strong correlation in their activation patterns (Sporns et al., 2004). Most research on age related changes in connectivity has focused on one of these networks; the default mode network (DMN).

The DMN is a network of brain areas that is more active while participants are not engaging in a specific task (i.e. in a resting state) than during task performance (Buckner et al., 2008; Greicius et al., 2003; Raichle et al., 2001). Brain areas belonging to the DMN are the precuneus, the medial prefrontal cortex, the superior frontal gyrus, the angular gyrus, the hippocampus and the middle temporal gyrus. Over a range of studies, during both task execution and resting state conditions, it has consistently been shown that connectivity within the DMN is significantly decreased with advancing age (Andrews-Hanna et al.,

2007; Damoiseaux et al., 2008; Grady et al., 2010; Sambataro et al., 2010). Moreover, this decrease in connectivity within the DMN has been linked to a deterioration in performance on processing speed and working memory tasks in elderly (Andrews-Hanna et al., 2007, Sambataro et al., 2010).

In addition, there is evidence, although less consistent, of age related changes in other networks. Fronto-parietal connectivity within both the dorsal attention network (DAN) and the frontoparietal control network (FPCN) was found to be reduced with aging (Andrews-Hanna et al., 2007; Rieckmann et al., 2011), whereas connectivity between frontal areas was increased (Rieckmann et al., 2011). These networks were argued to be involved in cognitive control (FPCN, Spreng et al., 2010; Vincent et al., 2008) and in overt and covert spatial attention and the creation of motor plans based on sensory inputs during task execution (DAN, Fox et al., 2005; Toro et al., 2008). Connectivity within the motor network was also found to be decreased during resting state (Wu et al., 2007).

Connectivity between networks also appears to be important for task performance. For example research has shown that the DMN and the dorsal attention network (DAN) generally tend to be anticorrelated; when activity in one network increases, activity in the other network decreases. This is in line with the function ascribed to these specific networks; while the DMN is less active during cognitive tasks, the DAN becomes more active during task execution (Fox et al., 2005). Two studies linked the anticorrelation between these networks to behavioral performance; participants with a stronger negative correlation, had less variable behavioral performance and performed better on a working memory task (Hampson et al., 2010; Kelly et al., 2008).

Although multiple functional networks have been discerned, most aging studies mainly focused on functional connectivity in one or a limited number of pre-specified networks. Instead, we were interested in the commonalities between connectivity changes in different networks; are the observed age-related changes in network connectivity characteristic for specific networks or is it possible to identify common patterns which are present in all or most of the networks? In addition, due to the focus on specific networks, most studies have looked at changes within this functional network, without taking into account connectivity between different networks. However, as previous studies have suggested (Park & Reuter-Lorenz, 2009; Rieckmann et al., 2011), the increase in neural activation that is often found with aging might be a sign of neural reorganization, which might affect the functional organization of networks identified mainly in young adults. Therefore looking at connectivity between networks is of crucial importance and will be the second focus of the present study.

The age related changes that have been found so far, were observed during task execution, as well as, during resting state. In the current study, seed regions for the functional connectivity analysis were selected based on areas involved in task performance.

Participants performed a visual oddball task which included novel stimuli. For the current purpose this task has several advantages. First of all, task difficulty is low, so both older and younger participants are able to perform well and to reach accuracy levels at ceiling. Second, adequate task performance in the oddball task requires continuous attentional control. Third, performance of visual oddball tasks generally recruits widespread areas in the occipital, parietal and frontal lobes (Kiehl et al., 2005). This enables us to use a broad range of areas that are involved in task performance and, more importantly, that are related to different functional networks, as a starting point for functional connectivity analysis.

In sum, in the present study we used areas involved in task performance to identify a range of functional networks and compared connectivity within these networks between young and elderly participants. Based on previous studies we expected to find age related reductions in connectivity within functional networks, especially within the DMN. Moreover, we examined age-related changes in functional connectivity between networks.

## 2.3 Methods

### 2.3.1 Participants

Twelve young participants (10 female, mean age 24.1,  $SD = 2.9$ ) and 30 older participants (10 female, mean age 63.9,  $SD = 6.2$ ) without a history of head injury or other neurological conditions participated in this study. All participants had normal or corrected to normal vision and a normal score (19 or 20) on the unabbreviated cognitive screening test for dementia (de Graaf & Deelman, 1991). Four of the elderly participants indicated that they used medication for high blood pressure, two elderly participants took medication against high cholesterol and one elderly participant took medication for diabetes. The study protocol was approved by the medical ethical committee of the University Medical Center Groningen and all participants gave written informed consent.

### 2.3.2 Task and Stimuli

Participants performed a visual oddball task. They were instructed to press a button with their right thumb when a target (letter 'X') appeared on the screen. No response was required when a standard (the letter 'O') or a novel (any of the other letters in the alphabet and digits 1-9) appeared on the screen. Three task versions were used. In the first version, only standard stimuli were presented; in the second version standard (probability 0.85) and target (probability 0.15) stimuli were presented and in the third version, standard

(probability 0.70), target (probability 0.15) and novel (probability 0.15) stimuli were presented. Each novel stimulus did not occur more than once per block. Three blocks of each task version were presented in a balanced random order, with the restriction that the task versions of consecutive blocks were dissimilar. Alternation of different task blocks was used to motivate participants to keep attention focused on the task. Participants were asked to fixate on the fixation cross during task performance and rest periods and to react as fast and accurately as possible.

Stimuli were generated on a Personal Computer using E-prime (Psychology Software Tools Inc., Pittsburgh, USA). They were presented on a screen positioned at the head end of the MRI scanner, which participants saw via a mirror attached to the head coil. Stimuli were presented in white, on a black background with a vertical visual angle of approximately 2 degrees, and a horizontal visual angle between 0.5 and 2 degrees, varying for the different symbols. Stimulus duration was 150 ms and inter-stimulus interval varied randomly between 1050 and 1450 ms (mean 1250 ms), resulting in approximately 128 stimuli per task block of three minutes. Task blocks were alternated with rest periods of 45 seconds.

### 2.3.3 Behavioral data

In addition to the fMRI experiment, all older participants completed a series of neuropsychological tests on a previous day. These tasks related to visual-motor sequencing (Trail making test A and B Reitan, 1958; Tombaugh, 2004), executive functioning (Stroop interference test, Stroop, 1935; Rule shift test, Behavioral Assessment of the Dysexecutive Syndrome, Wilson et al., 1996), working memory and incidental recall (forward and backward digit span, Wechsler Adult Intelligence Scale-Revised, Wechsler, 1981) and verbal learning (Dutch version of the Rey Auditory Verbal Learning Test, Lezak et al., 2004).

Data of one younger and one older participant, were excluded from the analysis because they did not comply with the task instructions. For four participants data of only two of the three task blocks were included in the analysis. For one participant, this was due to technical problems during data acquisition, the other three participants did not comply with the task instructions in one of the blocks. For each participant median reaction times ( $RT_{med}$ ) were calculated only for correct trials. Trials with RTs faster than 150 ms were regarded as fast guesses and were removed from the data. Differences between groups were assessed using the Mann-Whitney-U test, because the data were not normally distributed.

### 2.3.4 Recordings

Functional images were acquired using a 3T Philips Intera MRI scanner (Best, the Netherlands), using a standard transmit/receive head coil. The following pulse sequence parameters were used: fast field echo (FFE) single shot echo planar imaging (EPI); 46 slices; slice thickness 3.5 mm; no gap; field of view 224 mm; scanning matrix 64×64; transverse slice orientation; repetition time (TR) = 3 s; echo time (TE) = 35 ms; flip angle 90°. In addition, T1-weighted 3D FFE anatomical images of the entire brain were obtained with the following pulse sequence parameters: field of view 256 mm; scanning matrix 256×256; 120 slices; slice thickness 1 mm; transverse slice orientation; TE = 4.6 ms; TR = 25 ms; flip angle 30°.

### 2.3.5 fMRI data analysis

Functional imaging data were analyzed using Statistical Parametric Mapping software (SPM8; <http://www.fil.ion.ucl.ac.uk/spm>) implemented in Matlab 7.1.0 (The MathWorks, Natick, Massachusetts). Functional images were corrected for motion artifacts, coregistered to the T1 image, normalized to the Montreal Neurological Institute (MNI) standard template and smoothed with an 8-mm full-width at half-maximum (FWHM) Gaussian kernel. For the first-level statistical analysis of the fMRI data, the onsets of standard, target and novel trials were entered as separate regressors. Preliminary analysis of the data indicated that there were no differences in activation patterns between task versions, therefore stimuli were collapsed over task versions in order to optimize parameter estimation. Onsets of trials with incorrect responses were modeled as a separate regressor. Additionally, the realignment parameters and the first derivatives thereof were entered as covariates to correct for the effects related to head motion (Friston et al., 1996). No high-pass filter was applied because of the low-frequency cycling of conditions.

The task related regressors were convoluted with the canonical hemodynamic response function (HRF), the temporal derivative and the dispersion. When comparing BOLD signal changes in older and younger participants, changes in the timing and the shape of the HRF are a source of concern (Steffener et al., 2010). Therefore, we used an approach which combines the contribution of the three HRF terms by calculating the total area under the curve (see also Kokal et al., 2009). The area under the curve was calculated by reconstructing the fitted bold response for each of the stimulus categories, which were each subsequently integrated over time. This area under the curve value was fed into a factorial design in a second level analysis, containing a subject factor, the three stimulus categories, and the age groups (young and older participants). A family wise error correction (FWE) of 0.05 and a cluster extent of 20 voxels was used to identify regions in which there was a main effect of stimulus type. Interactions between stimulus type and participant group were investigated using an FWE cluster threshold of 0.05

(initial threshold  $p < 0.001$ ). Interpretation of results was restricted to gray matter areas.

### 2.3.6 Functional connectivity analysis

The procedure for the functional connectivity analysis mostly followed the approach described by Van Dijk et al. (2010). Seed regions were defined by a 4 mm sphere around voxels displaying peak activation in the F-contrast examining main effect of stimulus type over all groups. These seed regions were used for all participants. Because of the larger number of older, compared to younger participants this approach could lead to a bias toward the older participants in the selection of seed regions. To control for this possibility, we created separate F-contrasts for the young and older groups. Our aim was to find out how many significant voxels in the original F-contrast could be explained by voxels in the F-contrast for the younger or the older group, respectively. Therefore, we lowered the F-threshold for both the older and the younger maps until together they explained 98% of the voxels in the original map ( $F > 10$ ). Following this procedure, 39 % of the significant voxels could be attributed to voxels in the F-map of young participants, 44% to the F-map of older participants and 14% to both. This demonstrated that there is no bias in the selection of seed regions due to unequal group sizes.

Maps of functional connectivity were obtained by regressing the first eigenvariate of the time course from the seed region (corrected for the effects of stimulus onset) against the time courses of all acquired voxels. To minimize the effects of noise caused by the cardiac- and respiratory cycles, scanner drifts, and motion, the following nuisance regressors were included in the first level model: the realignment parameters and the first derivative of the realignment parameters, average white matter- and cerebral spinal fluid (csf) signals, and the mean whole brain signal. In addition stimulus onsets were included as nuisance regressors. White matter and csf voxels were defined using the apriori probability maps for various tissue types included in the SPM8 package. These were turned into binary maps by applying a threshold of 95% and 75% probability for white matter and csf, respectively. From these binary maps the average time courses for white matter and csf signals were extracted. Separate first level analyses were constructed for each of the seed regions. The regressors containing the first eigenvariate of the time course of the seed region were included in the second level models. All second level models included age group as independent variable. Main effects between groups were examined at a FWE cluster corrected threshold of 0.05 (initial threshold  $p < 0.001$ ).

### 2.3.7 Clustering of functional connectivity maps

Cluster analysis was used to group seed regions according to the similarity of their functional networks. This enabled us to compare our results to functional networks



previously presented in the literature and thereby clarify the interpretation of age related differences. For each seed region, a t-map was constructed representing the functional connectivity of that region with all voxels in the brain averaged over all participants. To reduce the dimensionality of the data, the Euclidian distance (or L2 norm) between the t-maps of each seed was calculated. The resulting distance matrix was fed into a K-means cluster analysis with 5000 repetitions and random starting points. A solution with 6 clusters was chosen based on the knee in the scree plot (Ding & He, 2004). Solutions with more clusters explained less than 5% additional variance. The clusters that were found were in accordance with functional networks as presented in the literature. In order to make one map on second level representing the functional connectivity within each resulting cluster, an additional functional connectivity analysis was performed on first level using the first eigenvariate extracted from the activation in the combined seed regions per cluster as the time course. For each cluster, a t-test was used to construct a functional connectivity map over groups. These maps were only used for comparing the functional networks to those in the literature; the assessment of group differences was done separately for each seed. To improve interpretability of the results and alignment with previous research, cluster membership of each seed is used in the presentation and discussion of the results. Membership as part of a functional network was determined for each area of which functional connectivity to the seed region changed depending on age group, through comparison with the cluster maps.

### 2.3.8 Corrections for gray matter volume

Additional analyses were carried out to determine whether the observed differences in functional connectivity could have been influenced by underlying differences in gray matter density or registration error (Oakes et al., 2007). First, voxel based morphometry (VBM) was used to identify regional brain volume of gray matter for each of the participants (Ashburner & Friston, 2000). Structural T1 images for each participant were segmented into gray matter (GM), white matter (WM), and cerebral spinal fluid (CSF) using tissue probability maps provided by SPM8. Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) was used to increase the accuracy of inter-subject alignment (Ashburner, 2007). Images were then normalized and modulated by the Jacobian determinants derived from the normalization step in order to adjust for the resulting volume changes due to normalization. Modulated normalized images were smoothed with a 10-mm FWHM Gaussian kernel. For statistical analysis, the two groups were combined in a one-way ANOVA, with the total intracranial volume (TIV) as a covariate to correct for individual differences in brain volume. TIV was calculated by summing volumes of GM, WM, and CSF derived from non-normalized segmented images. Because TIV in the present study includes CSF, it represents total brain volume and does not reflect atrophy of either GM or WM. Differences between young and elderly participants were examined with a threshold of  $P_{\text{FWE}} < 0.05$ , and a cluster extent of 15 voxels.

Second, the fMRI data were reanalyzed using gray matter density information of each participant as a voxel-dependent covariate. This was done using the robust regression procedure which is less sensitive to the effects of outliers (Yang et al., 2011) as implemented in the biological parametric mapping toolbox (Casanova et al., 2007). Although this robust procedure reduces the effects of outliers, we also noticed that it increased the voxel to (neighboring) voxel variability in the resulting T-map. For each of the areas that originally showed an effect of age on functional connectivity, we identified the number of voxels within that area that remained significant ( $p < 0.001$ ) if gray matter density was taken into account.

### 2.3.9 Connectivity and task performance

To evaluate the relation between changes in connectivity and cognitive functioning in the elderly group, the connectivity estimates were correlated with the performance on neuropsychological tests. Each score was converted into a z-score and reversed if required so that higher scores indicate better performance. The Spearman rank correlation coefficient was used instead of the Pearson correlation coefficient to cope with deviations from normality, linearity and to reduce effects of possible outliers. Because of the large number of multiple comparisons (9 test scores \* 28 connectivity estimates), we used a Monte Carlo resampling procedure to evaluate whether the number of significant correlations we detected was higher than could be expected by chance. The scores of participants were randomly permuted, and correlations with connectivity estimates were recomputed. The number of significant ( $p < 0.05$ ) positive correlations was stored. This procedure was repeated 5000 times to generate a null distribution. When the actual number of significant results was in the 5% tail of this distribution, we concluded that the number of significant differences was larger than could be expected based on chance. This was done separately for areas where older participants compared to young participants showed a) decreased connectivity and b) increased connectivity to the seed region. A subsequent question was whether the number of significant correlations differed significantly between regions with increased connectivity and regions showing decreased connectivity with age. Therefore, the number of significant clusters was compared between these two types of areas using a similar procedure.

## 2.4 Results

### 2.4.1 Behavioral Results

Older participants showed a tendency to respond slower (O,  $RT_{med} = 473$ , IQR=82) than younger participants, although this difference was not significant (Y,  $RT_{med} = 427$ , IQR =34;



$U(40)=215$ ,  $Z=1.68$ ,  $p=0.098$ ). The proportion of misses and false alarms was below 0.01% in both groups.

#### 2.4.2 Effects of task and age on fMRI activations

The first step in the analysis was to identify areas showing an effect of stimulus category (F-contrast); these areas were used in the functional connectivity analysis. Additionally, interactions between age group and stimulus category on brain activation were tested.

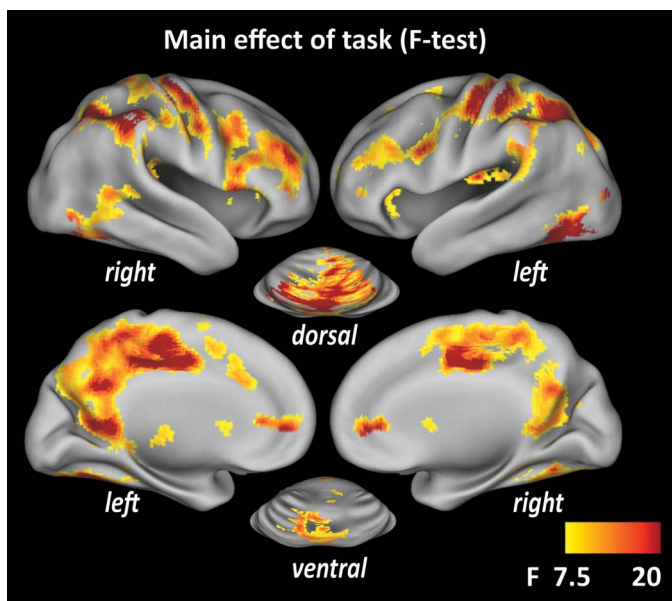


Figure 2.1: Areas showing a main effect of stimulus category are displayed ( $p_{\text{FWE}} < 0.05$ ). The top row shows the lateral view and the bottom row shows the medial view of the brain. Activations are displayed on an inflated surface rendering of the human brain using the CARET program (Van Essen et al., 2001).

Over all groups, increased activation in target and novel trials compared to standard trials was observed in the right precentral gyrus (BA44), the left and right inferior parietal lobules, the right middle frontal gyrus, and the right and left fusiform gyri. The right cerebellum pars 7 and the right inferior orbitofrontal gyrus showed more activation in target than standard trials. In addition, in particular the left inferior frontal operculum, the left middle occipital and the right inferior occipital gyrus, were more active in novel than in standard trials (see table 2.1 and figure 2.1). Furthermore, we found a number of areas where activation was decreased in target compared to standard and novel trials. These areas included the left postcentral gyrus, the right precentral gyrus (BA4), the mid cingulum, the left rolandic operculum, the right superior parietal gyrus, the left precuneus and the left calcarine sulcus. The right middle orbitofrontal gyrus and the left anterior cingulate were specifically less active in target than standard trials. Young participants showed decreased activation in target compared to standard trials in the left postcentral gyrus, the middle cingulum, the right fusiform gyrus and the left and right

superior temporal gyri, while there was no significant difference between these stimulus categories in the older participants (age group\*stimulus category, see supplementary table 2.1) .

Table 2.1: MNI coordinates for areas that show a main effect of stimulus category

Area	K	F	x y z	Cluster	Effect
L Precuneus (BA7)	228	23.68	-6 -56 34	DMN-p	S>T, N>T
L Calcarine (BA30)	167	24.76	-6 -52 8	DMN-p	S>T, N>T
R Middle Orbitofrontal (BA10)	85	23.45	10 46 -2	DMN-a	S>T
L Anterior Cingulate (BA10)	63	26.10	-10 48 -2	DMN-a	S>T
R Precentral3 (BA44)	26	18.12	40 4 32	FPCN	N>S, N>T
R Precentral2 (BA44)	54	20.38	50 12 42	FPCN	N>S, N>T
L Inferior Frontal Operculum (BA44)	45	23.88	-50 10 30	FPCN	N>S, N>T
R Middle Frontal (BA45)	198	27.49	44 48 20	FPCN	T>N, T>S
L Inferior Parietal (BA7)	726	33.06	-30 -54 46	FPCN	N>T, T>S
R Inferior Parietal (BA40)	782	42.61	54 -42 48	FPCN	T>N, N>S
R Superior Parietal (BA2)	60	20.78	18 -44 70	DAN-SMN	S>T, N>T
L Rolandic Operculum (BA48)	25	22.44	-38 -20 18	DAN-SMN	S>T, N>T
R Precentral (BA4)	456	34.82	46 -14 58	DAN-SMN	S>T, N>T
L Postcentral (BA3)	1150	44.28	-34 -30 62	DAN-SMN	S>T, N>T
L Mid Cingulum (BA23)	1184	53.57	-8 -22 46	DAN-SMN	S>T, N>T
R Cerebellum 7	20	20.31	8 -72 -44	DAN-VAN	T>N, T>S
L Middle Occipital (BA19)	72	25.23	-34 -84 14	DAN-VAN	N>S, N>T
R Fusiform (BA19)	186	27.57	38 -70 -20	DAN-VAN	N>S, T>S
R Inf Occipital (BA19)	67	31.12	34 -86 -8	DAN-VAN	N>S, N>T
L Fusiform (BA37)	1705	44.74	-44 -62 -16	DAN-VAN	N>T, T>S
R Inferior Orbitofrontal (BA38)	88	23.34	50 22 -6	COCN	T>N, T>S

L=left, R=right, BA=Brodmann's area, x,y,z=stereotactic coordinates, k=cluster extent, p=posterior, a=anterior, DMN=default mode network, VAN=visual attention network, FPCN=frontoparietal control network, DAN=dorsal attention network, SMN=somatomotor network, COCN=cingulo-opercular control network, S=standards, T=targets, N=novels

### 2.4.3 Functional Connectivity

In the second part of the analysis, we used functional connectivity analyses to examine differences in functional networks between older and younger participants. Areas showing a main effect of stimulus category were used as seed regions in this analysis. To facilitate comparisons with functional networks in the literature, functional connectivity maps of all seed regions were clustered. Seeds in each cluster were taken together to generate one functional connectivity map for each cluster on second level. Cluster membership of seed regions is presented in table 2.1. Below we will discuss the networks identified.

*Default mode network* The functional connectivity maps of the first and second cluster that were identified, closely resembled the default mode network (DMN, see e.g. Raichle

et al., 2001). In the first cluster connectivity to posterior parts of the DMN was most pronounced while in the second cluster connectivity to anterior parts was predominant. In both DMN clusters, seed regions showed functional connectivity to a network consisting of the precuneus (bilateral), superior (medial) frontal gyri extending on the left side into the middle frontal gyrus, the angular gyri, the left and right hippocampus and the middle temporal gyri (see figure 2.2).

*Fronto-parietal control network* The third cluster closely resembled the fronto-parietal control network (FPCN, Vincent et al., 2008). Areas belonging to this network were the right and left inferior parietal lobules, the right and left middle frontal gyri, the right and left inferior frontal operculum and inferior frontal triangular areas, the superior medial frontal gyrus, the supplementary motor area, and left and right caudate.

*Dorsal attention network* The networks of the fourth and fifth cluster contained areas involved in vision, attention and somatomotor processing which together closely resemble the DAN. The network of the fourth cluster contained the somatomotor parts of the DAN and closely resembles the previously identified somatomotor network (DAN-SMN, Beckmann et al., 2005; Damoiseaux et al., 2006). Functional connectivity from these seeds was found to the right and left superior temporal gyri, the right and left pre and postcentral gyri, the left and right superior parietal lobules, the left and right posterior insula, the paracentral lobule, the supplementary motor area and the mid cingulum. Primary and secondary visual processing areas, as well as inferior and superior parietal areas were the main components of the fifth cluster, subsequently called DAN-visual attention network (DAN-VAN). Seeds in this cluster showed functional connectivity to the left and right middle and inferior occipital gyrus, the left and right calcarine and lingual gyrus, bilateral cerebellar areas 6 ,7 and vermis 7 and 8 and the bilateral inferior and superior parietal lobules.

*Cingulo-opercular control network* Cluster 6 consisted of only one seed region, the right inferior orbitofrontal gyrus. The network of this seed region closely resembles the lateral parts of the cingulo-opercular control network (COCN, Dosenbach et al., 2007). Connectivity was found to the left and right inferior orbitofrontal gyri , the right and left inferior frontal opercula , the right and left superior temporal gyrus, the bilateral insula and the right middle temporal gyrus. Contrary to the findings of Dosenbach and colleagues, we did not observe any connectivity with the anterior cingulate.

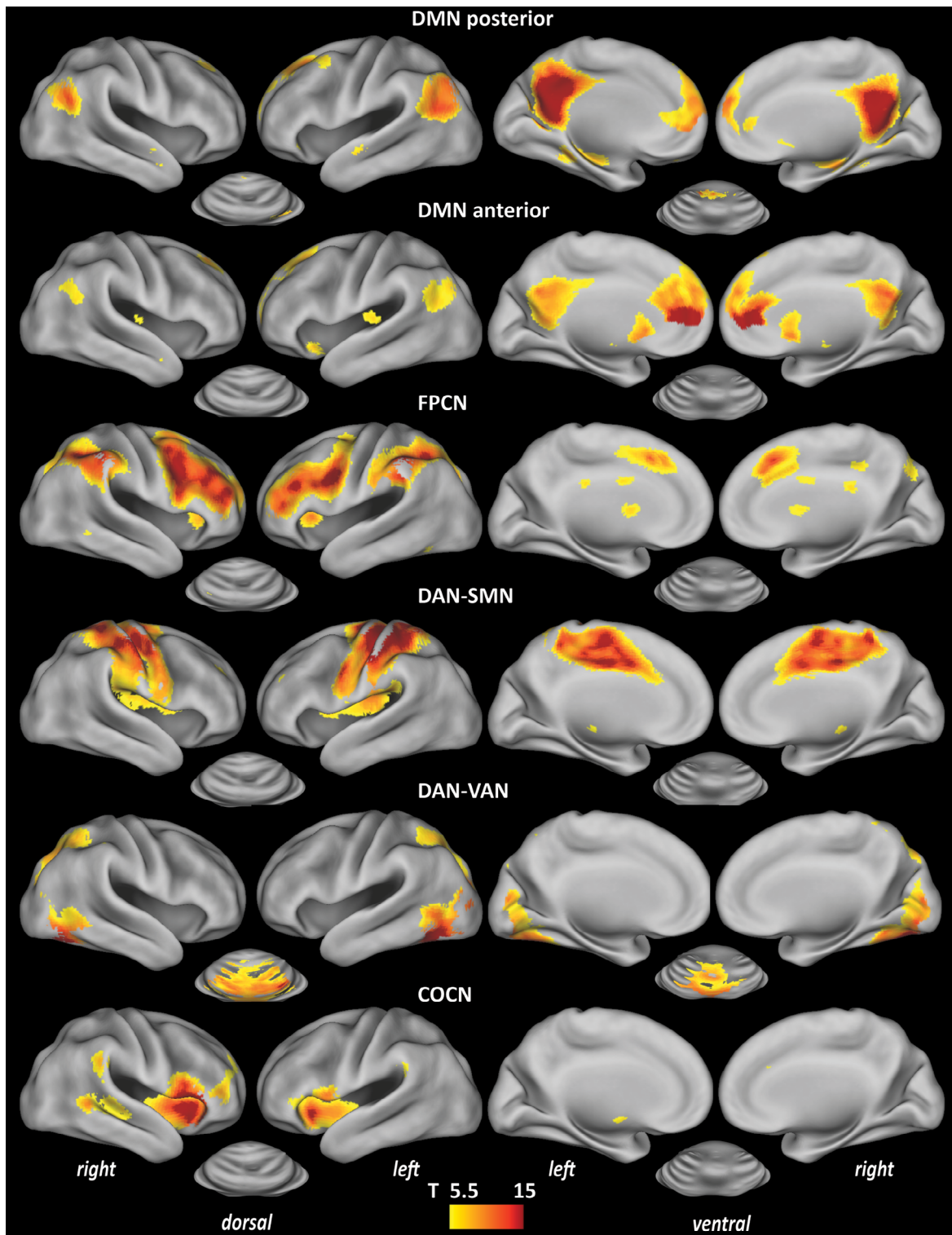


Figure 2.2: For each cluster the functional connectivity averaged over all participants, from the combined seed regions (using the first eigenvariate of all the seed voxels) to other voxels in the brain is displayed ( $P_{FWE} < 0.05$ ).



## 2.4.4 Effects of age on functional connectivity

For each seed region separately, effects of age on functional connectivity were examined. For reasons of clarity, the observed effects are grouped according to cluster membership of the seed.

The pattern that became clear from figure 2.3 and supplementary table 2.2 is that elderly show more connectivity to areas that do not belong to the functional network of the respective seed region than young participants. From seed regions in the DMN clusters, older participants showed more connectivity to areas belonging to the DAN-SMN (right and left rolandic operculi, supplementary motor area and anterior cingulate). From seeds in the FPCN elderly showed increased connectivity to areas belonging to the DMN, DAN-VAN and the DAN-SMN (precuneus, cuneus and middle cingulum, respectively). Seeds in the DAN-SMN showed increased connectivity to areas in the DMN and FPCN (precuneus, superior medial frontal gyrus and left inferior parietal lobule). The left middle occipital gyrus (DAN-VAN) seed showed increased connectivity to the left inferior parietal sulcus (FPCN). The COCN seed showed increased connectivity to the right insula (DAN-SMN) and the right calcarine sulcus (DMN). An exception to this pattern were two seed regions in the DAN-SMN which showed increased connectivity to the middle cingulum (within the DAN-SMN).

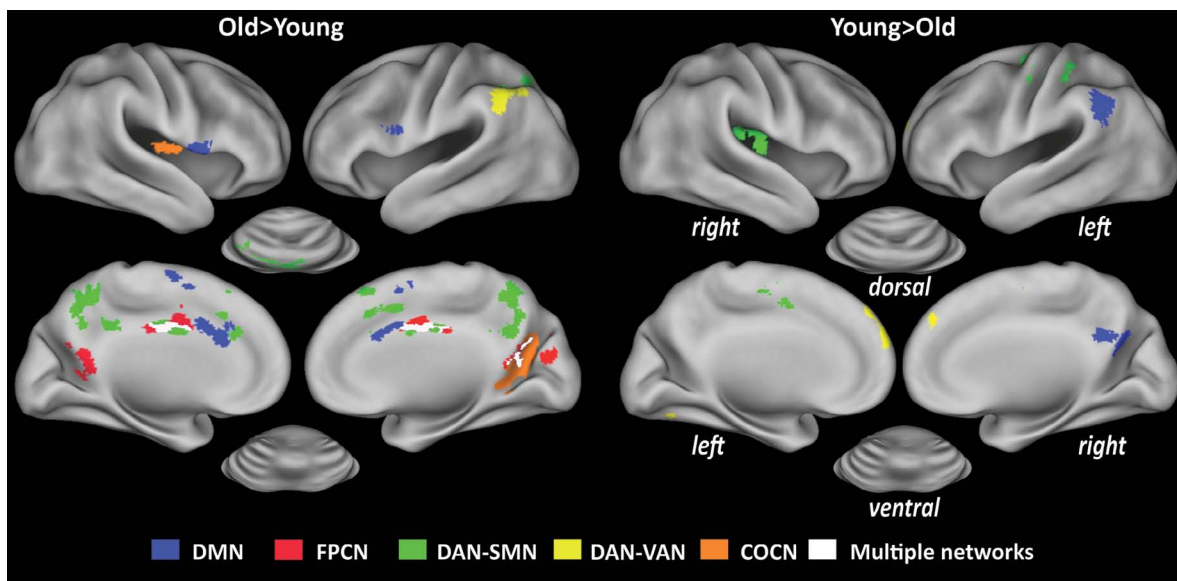


Figure 2.3: Effects of age on functional connectivity left: areas where elderly show more functional connectivity to the seed region than young participants (color represents cluster membership of the seed) right: areas where elderly show less functional connectivity to the seed region than young participants ( $p_{\text{FWE-cluster}} < 0.05$ ). Note that an area in a single color can indicate connectivity to one or multiple seeds within a cluster.

In addition, elderly showed reduced connectivity to areas within the network of the seed region, especially for the DMN and the DAN-SMN (see figure 2.3). From DMN seeds, there was reduced connectivity to the precuneus and the angular gyrus. From seeds in the DAN-SMN we found reduced connectivity to the right insula, the left pre and postcentral gyri and the right rolandic operculum. From DAN-VAN seeds, reduced connectivity was found to the left fusiform gyrus. Exceptions to this pattern were (a) the reduced connectivity in elderly to the right superior temporal gyrus from two DAN-SMN seeds; this area was not within any of the functional networks identified in the current study, and (b) reduced connectivity in elderly from the right inferior occipital gyrus (DAN-VAN) to the left superior frontal gyrus (DMN).

#### 2.4.5 Correction for gray matter density

VBM analyses showed significant decreases in gray matter in the older group compared to young participants, most notably in the anterior cingulate, the middle cingulum and the medial superior frontal gyrus (see figure 2.4). Additionally, gray matter losses were identified in the left middle frontal gyrus and the left frontal inferior and rolandic operculum. To try and disentangle the connectivity changes from the age related changes in gray matter density, connectivity analyses were repeated, using gray matter density as a voxelwise covariate (Oakes et al., 2007). Within each area that initially showed a significant effect of age on connectivity with one of the seed regions, the number of voxels which stayed above threshold ( $p < 0.001$ ) after gray matter correction is reported in supplementary table 2.3. Although a general decrease in the number of above-threshold voxels was observed, we found for all but two of the areas, significant differences between the two age groups in functional connectivity between different brain areas. The proportion of remaining voxels tended to be larger for areas showing an age related increase in connectivity compared to areas showing an age related decrease in connectivity with the seed region.

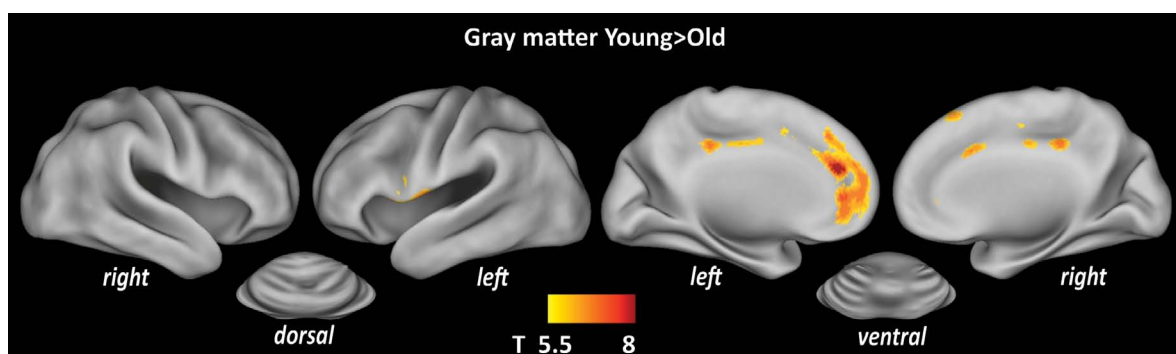


Figure 2.4: Areas showing decreased gray matter density in the elderly are displayed ( $p_{FWE} < 0.05$ ). The top row shows the lateral view and the bottom row shows the medial view of the brain.

### 2.4.6 Correlations between functional connectivity and neuropsychological test scores

All significant Spearman correlations between connectivity and neuropsychological test scores (NTs) are presented in supplementary table 2.2. In areas where older adults showed more connectivity than young adults, we observed 3 positive and 1 negative correlations between NTs and connectivity. That is, connectivity correlated positively with the digit span backwards (in two areas) and Stroop interference tests and negatively with the Rule shift task. Moreover, we found 8 positive correlations in areas where elderly showed less connectivity than young adults. Here, connectivity correlated positively with the Rule shift task (in three areas), the digit span forward and backward, the Rey Auditory Verbal Learning Task and part A of the Trail making test (in two areas).

The Monte Carlo resampling procedure was used to indicate whether the number of significant positive correlations between connectivity and NTs exceeded the amount expected by chance. This analysis revealed that connectivity correlated significantly with test scores for connections that were decreased in elderly compared to young participants. The number of correlations was not significant for the connections where elderly showed more connectivity than the young participants. In addition, we found that the difference between the number of significant correlations in the two types of areas was significantly larger than expected by chance.

## 2.5 Discussion

Although the present study used methods which were different from previous studies, the functional networks that were identified closely matched the networks that have previously been identified in the literature (see figure 2.2). This was true for studies using apriori defined seeds in seed based regression analyses (Fox et al., 2005; Vincent et al., 2008; Voss et al., 2010), as well as studies using independent component analysis (Beckmann et al., 2005; Damoiseaux et al., 2006; Rosazza & Minati, 2011). The fact that we were able to find the same networks using a more exploratory seed based approach along with a clustering method is a strong indication of the robustness of the networks that were identified.

Although seed based approaches usually identify the DAN as a single network (Fox et al., 2005; Vincent et al., 2008), we identified it in two subcomponents within this network. One component consisted of the somatomotor network, including the pre and postcentral gyri and the supplementary motor areas, while the other consisted of a visual attention network, including the occipital, calcarine and lingual gyri and the inferior and superior parietal lobules. These networks we identified closely resemble the identified networks in studies using independent component analyses (see for example figures 6b and 6d in Beckman et al, 2005). The reason for the discrepancy with other seed based correlation

studies might be related to specific task requirements; in our task the link between visual input, visual attention and response depended on the stimulus category. All three stimulus types provided the participants with visual input, while especially standard and novel stimuli captured attention and only target stimuli required a response.

The approach adopted in the present study allowed us to identify a consistent pattern of differences between older and younger participants in connectivity within and between the different functional networks identified. In general, older participants showed positive correlations between seed regions and areas which were located outside the functional network of that seed region. Moreover, in the DMN and the DAN-SMN, connectivity to areas within the functional networks of the seed region was reduced in older participants. These results suggest a general decrease in the specificity of functional networks in elderly.

Voss and colleagues (2010) found similar patterns of reductions in specificity of functional networks in elderly in the DMN, the FPCN and the DAN. They used a seed based approach with one a priori defined seed region for each of the networks. In their study, participants performed a series of passive viewing tasks. From the seed regions in all three networks, they found decreased connectivity in elderly to areas within the network and increased connectivity to areas outside the network. The similarity to our findings suggests that the pattern we identified was not specific to the visual oddball task that was used in the current study. Moreover, their results taken together with the current results, confirm that changes in connectivity in functional networks are not limited to specific networks but appear to be present in all networks identified. However, note that not all networks need to be affected to the same degree. At the moment it is not clear how differences between the tasks that participants perform affect the age related changes in connectivity that are detected. Therefore, it would be interesting to see whether these findings can be replicated resting state data or in more demanding cognitive tasks.

One possible explanation for the observed changes in connectivity in older individuals compared to our group of younger adults might be the decline in gray matter that is generally observed with age. In our elderly group, we observed age related declines in gray matter density mainly in the anterior cingulate, the middle cingulum and the rolandic operculum. This is in line with the gray matter changes observed in previous studies (Good et al., 2001). The functional connectivity analysis using voxelwise gray matter density as a covariate, remained to show connectivity differences similar to the differences originally identified, except for two areas. The resulting number of significant voxels was larger for areas showing an age related increase in connectivity compared to areas showing an age related decrease in connectivity with the seed region. These results show that the observed age related connectivity changes cannot be fully explained by the changes in gray matter.



An important question concerns the mechanism underlying the observed reduction in specificity of network connectivity. Dedifferentiation theory suggests that areas in the older brain may become less functionally distinct (Baltes & Lindenberger, 1997). This idea has been supported by a range of studies. It was, for example, found that distinct categories of visual stimuli activate less selective areas in elderly in the visual cortex (Park et al., 2004), as well as, in the parietal and prefrontal cortex (Carp et al., 2011a). Similarly, representations of distinct movements in the motor system, such as tapping the right and the left finger, are less selective in the elderly (Carp et al., 2011b). In addition, during visual imagery, the distinction between areas related to motion or faces was reduced in elderly (Kalkstein et al., 2011) and the specificity of the connections between the prefrontal cortex and the visual cortices during imagery was reduced in elderly. The current findings of reduced specificity in functional networks could be interpreted as a confirmatory evidence of dedifferentiation.

Changes in neural specificity can in some cases be related to changes in performance level; neural specificity in elderly for example was found to be a good predictor of fluid intelligence, but not crystallized intelligence (Park et al., 2010). The relation with performance level was partly confirmed in the current study. We found that decreased connectivity within the DMN and DAN-SMN was related to poorer performance on neuropsychological tests of visual-motor sequencing, executive functioning, working memory, incidental recall and verbal memory. However, we found no evidence of a negative or positive effect of increased connectivity between areas in different functional networks on task performance.

Over activations caused by dedifferentiation might be related to reduced specificity of functional networks. A recent study provided evidence for this idea; Langan et al. (2010) showed that reduced interhemispheric connectivity in elderly was related to a decreased ability to inhibit activity in the non-dominant hemisphere during unilateral motor task performance. It would be interesting to see if future studies in other domains will be able to link the decrease in specificity of neural representations to the specificity in functional networks, as well. Note however, that there are also a lot of studies showing positive relations between over activation in elderly and cognitive performance (for a review, Park and Reuter-Lorenz, 2009). In addition, we have shown in a recent electroencephalogram (EEG) study, using a selective attention task, that specific increases in connectivity in elderly can have a compensatory function (Geerligs et al., 2012b). Therefore, we agree with other researchers that aging theories need to incorporate both dedifferentiation and compensation to fully account for the age related changes on the neural level and their relation to cognitive performance (Carp et al., 2010).

Li and colleagues (2001) proposed that neural noise, defined as haphazard neuronal activity, might be the cause the reduction in the specificity of neural representations with age. An increase in neural noise with age might not only affect the specificity of neural

representations within specific brain areas, but also the specificity of functional networks. This is in line a recent simulation study showing that there seems to be an optimal level of neural noise, at which correlation within networks and anticorrelations between networks are highest. An increase or a decrease in noise with regard to this optimum reduces both correlations and anticorrelations (Deco et al., 2009). Therefore, we suggest that the increased levels of neural noise with age could be a plausible mechanism underlying both decreased connectivity within functional networks and increased connectivity between networks along with less specific neural representations.

In conclusion, we have shown a widespread decrease in the specificity of functional networks in older compared to younger participants. This was expressed in both an increase in connectivity between areas belonging to different functional networks and a decrease in connectivity between areas belonging to the same functional network. Specifically decreased connectivity within functional networks was related to poorer cognitive functioning in elderly.

## 2.6 Supplementary Tables

Supplementary table 2.1: Differences between groups in the effect of task condition (target-standard)

Area	k	T	x y z	Young standard Mean(SE)	Young target Mean (SE)	Old standard Mean(SE)	Old target Mean (SE)
L Postcentral (BA4)	7843	6.2	-46 -16 54	1.81(0.52)	-3.42(0.63)	1.72(0.35)	1.39(0.37)
L Mid Cingulum (BA31)		6.1	-2 -8 48				
L Mid Cingulum (BA24)		6.1	0 4 42				
L Sup Temporal (BA48)	434	5.9	-50 -22 14	0.72(0.36)	-2.12(0.44)	0.78(0.24)	1.23(0.26)
R Fusiform (BA19)	6618	5.8	22 -54 -12	0.61(0.39)	-1.79(0.47)	0.21(0.26)	1.27(0.28)
R Cerebellum VI		5.7	28 -52 -24				
R Cerebellum VI		5.5	20 -76 -18				
R Sup Temporal (BA22)	306	5.1	62 -10 8	0.96(0.48)	-2.35(0.58)	0.64(0.32)	1.07(0.34)

L=left, R=right, BA=Brodmann's area, x,y,z=stereotactic coordinates, k=cluster extent, Y=young participants, O=older participants

## Functional connectivity in the aging brain during task performance

Supplementary table 2.2: Group differences in functional connectivity and correlations with neuropsychological test scores

Seed region	Cluster (seed)	Connectivity with area	Cluster (area)	k	T	x y z	effect	Young mean (SE)	Old mean (SE)	task (r)
L Calcarine (BA30)	DMN-P	R Rolandic Oper (BA48)	DAN-SMN/COCN	198	4.5	58 6 2	O>Y	-0.19(0.02)	-0.04(0.02)	RS (-.38) DSP(.45)
L Precuneus (BA7)	DMN-P	L A Cingulate (BA24)	DAN-SMN/FPCN	404	4.2	0 24 28	O>Y	-0.16(0.02)	0(0.03)	DSP(.45)
L A Cingulate (BA10)	DMN-A	L Rolandic Oper (BA48)	DAN-SMN/FPCN	202	4.7	-54 4 16	O>Y	-0.09(0.01)	0.04(0.01)	
L A Cingulate (BA10)	DMN-A	L Supplementary Motor Area (BA6)	DAN-SMN	244	4.7	-2 4 60	O>Y	-0.17(0.03)	0.01(0.02)	
R Mid Orbitofrontal (BA10)	DMN-A	White matter extending into L Sup Orbitofrontal (BA47)	Part FPCN	166	5.4	-26 42 0	O>Y	-0.02(0.02)	0.09(0.01)	
L Inf Frontal Oper (BA44)	FPCN	R Cuneus (BA19)	DAN-VAN	225	4.7	8 -84 24	O>Y	-0.16(0.02)	0(0.02)	
R Mid Frontal (BA45)	FPCN	Calcarine/Precuneus (BA30)	DMN	435	5.2	0 -56 10	O>Y	-0.37(0.04)	-0.11(0.03)	
R Precentral3 (BA44)	FPCN	L Mid Cingulum (BA24)	DAN-SMN	306	5.7	0 0 40	O>Y	-0.03(0.03)	0.14(0.02)	
L Mid Cingulum (BA23)	DAN-SMN	L Mid Cingulum (BA23)	DAN-SMN/FPCN	213	6.3	0 -14 36	O>Y	0.04(0.04)	0.26(0.02)	
L Mid Cingulum (BA23)	DAN-SMN	R Precuneus (BA5)	DMN	699	5.6	6 -56 56	O>Y	-0.08(0.02)	0.15(0.03)	
L Mid Cingulum (BA23)	DAN-SMN	L Cerebellum Crus 1	DAN-VAN	239	5	-34 -66 -28	O>Y	-0.23(0.02)	-0.04(0.03)	
L Postcentral (BA3)	DAN-SMN	R Sup Medial Frontal (BA32)	FPCN	347	4.9	12 24 44	O>Y	-0.03(0.02)	0.1(0.01)	
L Postcentral (BA3)	DAN-SMN	L Inf Parietal (BA40)	FPCN	203	4.8	-46 -50 54	O>Y	-0.03(0.01)	0.07(0.01)	
L Rolandic Oper (BA48)	DAN-SMN	R Precuneus (BA23)	DMN	488	4.6	8 -58 32	O>Y	-0.11(0.02)	0.03(0.02)	
R Sup Parietal (BA2)	DAN-SMN	R Mid Cingulum (BA32)	DMN	252	4.6	4 32 32	O>Y	-0.13(0.03)	0.04(0.02)	
L Mid Occipital (BA19)	DAN-VAN	L Inf Parietal (BA40)	FPCN	213	4.9	-44 -64 48	O>Y	-0.12(0.02)	0.01(0.02)	STI(.39)
R Inf Orbitofrontal (BA38)	COCN	R Calcarine (BA17)	DMN	968	6.6	24 -60 18	O>Y	-0.15(0.01)	0.01(0.02)	
R Inf Orbitofrontal (BA38)	COCN	R Insula (BA48)	DAN-SMN/DMN	210	4.2	40 -10 10	O>Y	-0.03(0.02)	0.1(0.02)	

Supplementary table 2.2 continued: Group differences in functional connectivity and correlations with neuropsychological test scores

Seed region	Cluster (seed)	Connectivity with area	Cluster (area)	k	T	x y z	effect	Young mean (SE)	Old mean (SE)	task (r)
L Precuneus (BA7)	DMN-P	L Angular (BA39)	DMN	425	5.5	-54 -58 38	Y>O	0.19(0.02)	0.09(0.01)	
L A Cingulate (BA10)	DMN-A	R Precuneus (BA23)	DMN	234	4.5	10 -62 26	Y>O	0.31(0.04)	0.17(0.02)	
L Mid Cingulum (BA23)	DAN-SMN	R Sup Temporal (BA48)	none	282	4.7	50 -28 12	Y>O	0.13(0.02)	0.03(0.03)	
L Rolandic Oper (BA48)	DAN-SMN	R Insula (BA48)	DAN-SMN	174	5.3	38 0 14	Y>O	0.17(0.01)	0.09(0.01)	RS(.58)
L Rolandic Oper (BA48)	DAN-SMN	L Precentral (BA6)	DAN-SMN	347	5.2	-18 -14 58	Y>O	0.14(0.02)	0.06(0.02)	RS(.41)
L Rolandic Oper (BA48)	DAN-SMN	L Postcentral (BA4)	DAN-SMN	229	4.9	-50 -18 52	Y>O	0.16(0.02)	0.07(0.01)	
R Precentral (BA4)	DAN-SMN	R Rolandic Oper (BA48)	DAN-SMN	182	4.8	40 -16 20	Y>O	0.12(0.03)	0.02(0.02)	DSF(.50)
R Sup Parietal (BA2)	DAN-SMN	R Sup Temporal (BA48)	none	232	4.8	44 -18 10	Y>O	0.14(0.04)	-0.01(0.03)	WD(.39) DSB(.43) TRA(.51)
L Mid Occipital (BA19)	DAN-VAN	L Fusiform (BA37)	DAN-VAN	170	5.7	-38 -58 -10	Y>O	0.2(0.02)	0.1(0.01)	RS(.40)
R Inf Occipital (BA19)	DAN-VAN	L Sup Frontal (BA9)	DMN	381	4.3	-14 56 26	Y>O	0(0.03)	-0.09(0.03)	TRA(.45)

The outer right column shows significant correlations between connectivity and task performance in the elderly group. L=left, R=right, BA=Brodmanns area, x,y,z=stereotactic coordinates, k=cluster extent, Y=young participants, O=older participants, P=posterior, A=anterior, Inf=Inferior, Sup=superior, Mid=Middle, Oper=Operculum, DMN=default mode network, VAN=visual attention network, DAN=dorsal attention network, FPCN=frontoparietal control network, SMN=somatomotor network, COCN=cingulo-opercular control network, DSF=digit span forward, DSB=digit span backward, TRA=trialmaking test part A, RS=ruleshift task, WD= 15 word test direct recall, STI=Stroop interference

## Functional connectivity in the aging brain during task performance

Supplementary table 2.3: Group differences in functional connectivity after corrections for gray matter density

Seed region	Cluster (seed)	Connectivity with area	Cluster (area)	k	T	x y z	effect	T after GMC	k	Percentage of original voxels
L Calcarine (BA30)	DMN-P	R Rolandic Oper (BA48)	DAN-SMN/ COCN	198	4.5	58 6 2	O>Y	4.74	127	64.1
L Precuneus (BA7)	DMN-P	L A Cingulate (BA24)	DAN-SMN/ FPCN	404	4.2	0 24 28	O>Y	5.25	124	30.7
L A Cingulate (BA10)	DMN-A	L Rolandic Oper (BA48)	DAN-SMN/ FPCN	202	4.7	-54 4 16	O>Y	4.29	68	33.7
L A Cingulate (BA10)	DMN-A	L Supplementary Motor Area (BA6)	DAN-SMN	244	4.7	-2 4 60	O>Y	5.2	148	60.7
R Mid Orbitofrontal (BA10)	DMN-A	White matter extending into L Sup Orbitofrontal (BA47)	Part FPCN	166	5.4	-26 42 0	O>Y	4.71	39	23.5
L Inf Frontal Oper (BA44)	FPCN	R Cuneus (BA19)	DAN-VAN	225	4.7	8 -84 24	O>Y	5.91	218	96.9
R Mid Frontal (BA45)	FPCN	Calcarine/Precuneus (BA30)	DMN	435	5.2	0 -56 10	O>Y	5.46	228	52.4
R Precentral3 (BA44)	FPCN	L Mid Cingulum (BA24)	DAN-SMN	306	5.7	0 0 40	O>Y	8.3	207	67.6
L Mid Cingulum (BA23)	DAN-SMN	L Mid Cingulum (BA23)	DAN-SMN/ FPCN	213	6.3	0 -14 36	O>Y	5.5	175	82.2
L Mid Cingulum (BA23)	DAN-SMN	R Precuneus (BA5)	DMN	699	5.6	6 -56 56	O>Y	5.5	401	57.4
L Mid Cingulum (BA23)	DAN-SMN	L Cerebellum Crus 1	DAN-VAN	239	5	-34 -66 -28	O>Y	4.85	107	44.8
L Postcentral (BA3)	DAN-SMN	R Sup Medial Frontal (BA32)	FPCN	347	4.9	12 24 44	O>Y	4.71	205	59.1
L Postcentral (BA3)	DAN-SMN	L Inf Parietal (BA40)	FPCN	203	4.8	-46 -50 54	O>Y	4.35	36	17.7
L Rolandic Oper (BA48)	DAN-SMN	R Precuneus (BA23)	DMN	488	4.6	8 -58 32	O>Y	4.5	202	41.4
R Sup Parietal (BA2)	DAN-SMN	R Mid Cingulum (BA32)	DMN	252	4.6	4 32 32	O>Y	4.56	78	31.0
L Mid Occipital (BA19)	DAN-VAN	L Inf Parietal (BA40)	FPCN	213	4.9	-44 -64 48	O>Y	5	176	82.6
R Inf Orbitofrontal (BA38)	COCN	R Calcarine (BA17)	DMN	968	6.6	24 -60 18	O>Y	5.63	664	68.6
R Inf Orbitofrontal (BA38)	COCN	R Insula (BA48)	DAN-SMN/ DMN	210	4.2	40 -10 10	O>Y	4.94	132	62.9

Supplementary table 2.3 continued: Group differences in functional connectivity after corrections for gray matter density

Seed region	Cluster (seed)	Connectivity with area	Cluster (area)	k	T	x y z	effect	T after GMC	k after GMC	Percentage of original voxels
L Precuneus (BA7)	DMN-P	L Angular (BA39)	DMN	425	5.5	-54 -58 38	Y>O	4.97	59	13.9
L A Cingulate (BA10)	DMN-A	R Precuneus (BA23)	DMN	234	4.5	10 -62 26	Y>O	7.11	20	8.5
L Mid Cingulum (BA23)	DAN-SMN	R Sup Temporal (BA48)	none	282	4.7	50 -28 12	Y>O	5.02	59	20.9
L Rolandic Oper (BA48)	DAN-SMN	R Insula (BA48)	DAN-SMN	174	5.3	38 0 14	Y>O	3.34	1	0.6
L Rolandic Oper (BA48)	DAN-SMN	L Precentral (BA6)	DAN-SMN	347	5.2	-18 -14 58	Y>O	4.52	102	29.4
L Rolandic Oper (BA48)	DAN-SMN	L Postcentral (BA4)	DAN-SMN	229	4.9	-50 -18 52	Y>O	3.49	9	3.9
R Precentral (BA4)	DAN-SMN	R Rolandic Oper (BA48)	DAN-SMN	182	4.8	40 -16 20	Y>O	3.54	2	1.1
R Sup Parietal (BA2)	DAN-SMN	R Sup Temporal (BA48)	none	232	4.8	44 -18 10	Y>O	--	--	0.0
L Mid Occipital (BA19)	DAN-VAN	L Fusiform (BA37)	DAN-VAN	170	5.7	-38 -58 -10	Y>O	4.22	44	25.9
R Inf Occipital (BA19)	DAN-VAN	L Sup Frontal (BA9)	DMN	381	4.3	-14 56 26	Y>O	--	--	0.0

L=left, R=right, BA=Brodmanns area, x,y,z=stereotactic coordinates, k=cluster extent, Y=young participants, O=older participants, P=posterior, A=anterior, Inf=Inferior, Sup=superior, Mid=Middle, Oper=Operculum, DMN=default mode network, VAN=visual attention network, DAN=dorsal attention network, FPCN=frontoparietal control network, SMN=somatomotor network, COCN=cingulo-opercular control network, GMC=corrections for gray matter density



# Chapter 3

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A graph theoretical study of functional connectivity in the aging brain during resting state

Submitted as:

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A brain wide study of age-related changes in functional connectivity.

## 3 A graph theoretical study of functional connectivity in the aging brain during resting state

### 3.1 Abstract

Aging affects functional connectivity between brain areas, however, a complete picture of how aging affects integration of information within and between functional networks is missing. We used complex network measures, derived from a brain-wide graph, to provide a comprehensive overview of age-related changes in functional connectivity. Functional connectivity in young and older participants was assessed during resting state fMRI. The results show that aging has a large impact, not only on connectivity within functional networks but also on connectivity between the different functional networks in the brain. Brain networks in the elderly showed decreased modularity (less distinct functional networks) and decreased local efficiency. Connectivity decreased with age within networks supporting higher level cognitive functions, that is, within the default mode, cingulo-opercular and fronto-parietal control networks. Conversely, no changes in connectivity within the somatomotor and visual networks, networks implicated in primary information processing, were observed. Connectivity between these networks even increased with age. A brain-wide analysis approach of functional connectivity in the aging brain thus seems fundamental in understanding how age affects integration of information.

### 3.2 Introduction

Performance in various domains of cognitive functioning has been found to decline with age (Grady, 2012). There is evidence that these deteriorations are partly related to changes in communication between different brain areas (Andrews-Hanna et al., 2007; Sambataro et al., 2010). We previously found the first evidence that aging not only affects functional connectivity within specific functional networks, implicated in particular cognitive functions, but communication between different functional networks as well (Geerligs et al., 2012a). In the current study, we investigated how aging affects the integration of information across the whole brain, that is, within as well as between functional brain networks.

Whole brain analysis requires a novel approach. So far, effects of aging on functional connectivity have mainly been assessed using seed based functional connectivity and independent component analysis (Biswal et al., 1995; Fox et al., 2005; van de Ven et al., 2004). Both methods have a limited capability of providing a complete view of the characteristics of connectivity between and within functional networks. Seed based connectivity requires a hypothesis regarding the chosen seed region, while independent

component analysis has the inherent limitation that only connectivity within functional networks can be examined. In the current study we apply complex network measures, based on social network analysis, to assess connectivity within a brain wide graph of functional areas (Power et al., 2011; Rubinov & Sporns, 2010).

In the context of a graph, brain areas are referred to as nodes and connections between nodes are referred to as edges. Nodes that are directly connected through one edge are referred to as neighbors, whereas a series of edges connecting distant nodes are referred to as a path. After a network has been defined in such a way, it is possible to extract different complex network measures that characterize the connectivity structure of the network. This approach has major advantages over a mass-univariate approach in which all connections between all areas are tested independently. First of all, graph theory avoids the large number of multiple comparisons that accompany a mass-univariate approach. Second, by examining complex network measures, specific features that are important for the functioning of the network can be assessed.

Studies in younger adults have shown that the brain consists of a number of separate functional networks. There are dense connections within these networks whereas connectivity between different networks is sparse. This organization is thought to benefit specialized or segregated information processing in different brain networks (Bullmore & Sporns, 2012). The extent to which such an organization is present can be measured with the complex network measure modularity (Newman, 2004). There are indications that functional brain networks in elderly become less distinct, due to an increase in inter-network connections along with a decrease in intra-network connections (Geerligs et al., 2012a). Previous studies have already shown that brain areas become functionally dedifferentiated with advancing age (Baltes & Lindenberger, 1997; Carp et al., 2011a; Dennis & Cabeza, 2011; Park et al., 2004). Geerligs et al. (2012a) extended these findings by showing that dedifferentiation might also occur on the level of large scale functional brain networks. One of the goals of the current study was to lend more support to these findings, using complex network measures. If functional networks indeed become dedifferentiated with age, we would expect a reduction in modularity. A reduction in modularity with age might be driven by global changes throughout the networks or by decreased connections within or increased connections between specific functional networks. To examine these possibilities, we additionally examined the participation coefficient (Guimerà & Amaral, 2005), which is a local measure of the proportion of inter- and intra-network connections.

The trajectory between the input and the output of the brain, that is, between perception and overt and covert behavior, requires the integration of information within, as well as between, different functional networks. The capacity to integrate information across all brain areas can be assessed with global efficiency (Latora & Marchiori, 2001). Higher level functions, such as executive functions, that require integration of information

from different sources, benefit from global efficiency across the whole network (Bullmore & Sporns, 2012). In addition, primary processing functions, such as visual information processing benefit from clustered connections between neighboring nodes. This can be measured using local efficiency, which quantifies connections between neighboring nodes (Latora & Marchiori, 2001). If neighboring nodes are well connected, information exchange will be more segregated as well as more efficient and the networks will be more resilient to disruptions in connectivity.

Previous studies using graph theory in fMRI data have shown that aging is accompanied by a reduction in global and local network efficiency (Achard & Bullmore, 2007). Modularity on the other hand was reported to be similar in older and younger participants (Meunier et al., 2009a). In the current paper, we extend these previous findings by examining age-related effects on complex networks measures within different functional networks. Because each functional network tends to be related to a specific cognitive function, this approach allows for a more direct link between the changes in complex graph measures and the changes in cognitive functioning. In this paper, we used the network measures described above to provide a coherent whole brain view of age-related changes in functional connectivity. To extract functional networks in the older and younger groups, we used data driven methods which did not require any a-prior hypotheses about specific features of these networks. We found that, the balance between intra- and inter-network connections shifted with age, as reflected by decreased modularity. Changes in local efficiency varied across networks. In the visual and somatomotor networks, subserving more elementary cognitive functions, efficiency was maintained in elderly, whereas a sharp decrease in efficiency was found in higher level processing networks, the default mode network (DMN, Buckner et al., 2008; Greicius et al., 2003; Raichle et al., 2001), fronto-parietal control network (FPCN, Spreng et al., 2010; Vincent et al., 2008) and the cingulo-opercular network (Dosenbach et al., 2007).

### 3.3 Methods

#### 3.3.1 Participants

Forty older adults (24 males,  $M_{\text{age}} = 64.9$  years, age range: 59-74 years) and 40 younger adults (21 males,  $M_{\text{age}} = 20.6$  years, age range: 18-26 years) participated in this experiment. All participants were right handed and had no history of neurological or psychiatric disorders. Older participants had a score of 26 or higher on the Mini Mental Status Examination (MMSE, Folstein et al., 1975) and below 16 on each of the subscales of the Hospital Anxiety and Depression Scale (HADS, Zigmond & Snaith, 1983). All participants had normal or corrected-to-normal visual acuity. The study adhered to the Declaration of Helsinki and was approved by the local ethics committee of the University Medical Center

Groningen, the Netherlands. Informed consent was obtained from all participants. Data of one older participant was lost due to technical problems. One older participant was excluded because a brain abnormality was detected.

### 3.3.2 Data acquisition and preprocessing

FMRI scans were obtained during 10 minutes of resting state with a three tesla MR scanner (3T Achieva, Philips Medical Systems, Best, Netherlands), with echo planar imaging (EPI) capability and an eight channel SENSE head coil. Participants were instructed to keep their eyes closed and not fall asleep. Functional images were obtained with the following pulse sequence parameter settings: single shot EPI; 37 slices; slice thickness 3.5 mm; no gap; field of view 224 mm; matrix scan size 64 by 64; transverse slice orientation; repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; minimal temporal slice timing (1836 ms); flip angle 70°. A 3D T1-weighted anatomical scan of the entire brain was obtained for each participant using the following pulse sequence parameters: field of view 256 mm; matrix scan size 256 by 256; 170 slices; slice thickness 1 mm; transverse slice orientation; TE = 3.6 ms; TR = 9 ms; flip angle 8°. Offline processing was performed using the statistical parametric mapping software package (SPM 8; <http://www.fil.ion.ucl.ac.uk/spm/software>). First, for each participant, the functional images were motion-corrected and co-registered to the anatomical scan. Co-registration was checked visually and adjusted manually when required. Smooth signal intensity variations due to field inhomogeneities were reduced in both structural and functional images by applying bias regularization as implemented in SPM. For functional images, the regularization was initially applied only to the first and the last functional scan. Based on these two corrections, an average correction factor was computed for each voxel, which was applied to all scans. A study specific anatomic template was created (for young and elderly participants together), using Diffeomorphic Anatomical Registration Exponentiated Lie algebra (DARTEL), to optimize inter-participant alignment (Ashburner, 2007). Data were smoothed with an 8 mm full-width half maximum (FWHM) Gaussian kernel.

For the functional connectivity analyses, additional preprocessing steps were used to remove spurious variance from the time courses. One of these steps was global signal regression. The global signal is assumed to reflect a combination of resting-state fluctuations, physiological noise (e.g. respiratory and cardiac noise), and other noise signals (Birn et al., 2006). It has been shown that (physiological) noise in the BOLD signal increases with advancing age (D'Esposito et al., 1999; Makedonov et al., 2013). Therefore, in the current study, we applied global signal regression to reduce these effects of noise differences between groups on estimates of the correlation coefficient. Using SPM routines, a multiple regression approach was used which included regression of the time-courses from the white matter, cerebro-spinal fluid and the whole brain (global signal) and regression of motion parameters (for details of this procedure see Geerligts et al.,

2012a). First derivatives of these signals were also regressed out. In addition, a high pass filter (time constant of 111 seconds) was applied.

It has been shown that participant motion can have large effects on functional connectivity estimates (Power et al. 2012). To minimize such effects, scans which might have been affected by movement were excluded from the analysis (similar to the procedure described in Power et al., 2012). The first step in this correction was to calculate the total displacement per scan. The rotational parameters were transformed to millimeters (mm) displacement by assuming affected voxels were at a distance of 65 mm from the origin of the rotation. The total displacement per scan was computed using the procedure in the ArtRepair toolbox <http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html>. Scans in which the displacement compared to the previous scan was larger than 0.5 mm were flagged. The second step in the correction was to identify scans which could have been affected by participant motion by examining changes in the intensity of the functional image. For each voxel (within the participant specific brain mask) a temporal derivative of the signal was calculated, by computing the intensity difference between subsequent scans. Subsequently, the root mean square (RMS) intensity change over all voxels was calculated as index of total intensity change. Scans in which the RMS was higher than 3 standard deviations above the average were flagged (Shannon et al., 2011; Smyser et al., 2010). For functional connectivity analysis, all flagged scans were excluded, as well as the scan before and two scans after the flagged scan. Two younger and two older participants with less than 200 remaining scans were excluded. In the remaining younger participants an average of 10.4% of all scans was removed based on this procedure, in the older participants the proportion of removed scans was 7.2% on average.

### 3.3.3 Functional connectivity analysis

For functional connectivity analysis the brain wide graph of 264 putative functional areas (10 mm diameter spheres) created by Power and colleagues (2011) was used. The functional areas in this graph were defined based on meta-analysis and functional connectivity mapping so that each area represents an element of brain organization. To make sure that the graph only included areas that did not suffer from susceptibility artifacts, a group mask was created. First, participant-specific binary images were created by thresholding functional images at 70% of mean signal intensity. A group mask was created by multiplying the binary images of all participants. If the group mask overlapped less than 50% with a functional area, this area was excluded from analysis (i.e. 29 functional areas). Average time courses were extracted for the remaining 235 functional areas. Pearson correlation coefficients were computed between the time courses of all functional areas in each participant separately. To remove connections which might be due to re-slicing or motion-induced artifacts, correlations between areas less than 20 mm

apart were set to zero (Power et al., 2011). The diagonal of the correlation matrix was set to zero to remove correlations between an area and itself.

### 3.3.4 Thresholding

Based on the correlation matrix, graphs were constructed for each participant. Graph characteristics, such as modularity and global efficiency are affected by the number of nodes, but also by the number of edges in a graph (van Wijk et al., 2010). For each participant, the correlation matrix was thresholded to enhance the contrast between relevant (strong) and irrelevant (weak) connectivity values. This was done in such a way that the number of edges in the graph was constant. A threshold was selected using the method below, in order to maximize the amount of information obtained about the network on the group level.

For a range of thresholds (selecting between 1 - 50 % strongest connections), and for both age groups separately, we applied the following procedure. For each participant, the correlation matrix was binarized by setting the connections above the pre-defined threshold to 1 and all other connections to zero. Subsequently these binarized matrixes were averaged over all participants within each group. This averaged matrix is referred to as the 'actual' matrix. Information theory was applied to compute the entropy over the actual matrix (Shannon, 1948). The threshold at which the entropy is lowest, is the threshold at which the actual matrix contains the least disorder and therefore the largest stability over participants. However, the entropy also depends on the number of elements taken into account for each participant; at a threshold of 100% the entropy will be zero. Therefore, a correction was applied to account for these changes by comparing the entropy in the actual matrix to the entropy in a randomized matrix. We created 50 randomized matrices per participant, per threshold, preserving the number of nodes and the degree distribution (Maslov & Sneppen, 2002). These random graphs were used to construct 500 new average graphs, by randomly sampling one of the 50 randomized networks per participant. The entropy was computed for each of these average random matrices and averaged. Then, the difference between the entropy in the actual and the entropy in the random matrices was computed. Once this procedure was performed for all thresholds, the optimal threshold was defined as the threshold at which the difference between the entropy in the actual matrices and the entropy in the randomized matrices is maximal. The optimal threshold is found when the information in the actual matrix is as unique as possible (i.e., highest stability across subjects), and more importantly, least resembles the result for a random network. More details of this method, including simulations, are presented in the supplementary materials. Applying the procedure described above to both age groups separately, resulted in a threshold set at the 2.8 % strongest connections in the network for the younger participants and 2.6% for the older participants. Therefore, a threshold of 2.7 % was selected (see supplementary figure 3.2).



### 3.3.5 Graph analysis

Network measures were calculated using functions implemented in the Brain Connectivity Toolbox (Rubinov & Sporns, 2010, [www.brain-connectivity-toolbox.net](http://www.brain-connectivity-toolbox.net)). Modularity is the extent to which a graph can be divided into modules with a large number of within module connections and a minimal number of between module connections (Girvan & Newman, 2002). For fMRI data, such modules are similar to the functional networks that can be identified using seed based correlations or independent component analysis (Power et al., 2011). Network modularity estimates were computed using the algorithm by Blondel and colleagues (2008), using the average modularity across 50 runs of the algorithm. In addition, local and global efficiency were assessed (Latora & Marchiori, 2001). Global efficiency is the inverse of the average shortest path length in the network and is suitable for use in disconnected networks. Local efficiency is the inverse of the average shortest path length between all immediate neighbors of a node. Local efficiency tends to be related to modularity; networks which have dense local connections tend to have a more modular organization (Bullmore & Sporns, 2012). Local efficiency was averaged over all nodes to estimate the mean local efficiency for the complete graph or specific networks.

The graph was partitioned into modules separately for younger and older participants. As input to the partitioning algorithm, we computed averages of the binary matrices of all participants (correlation matrices thresholded at 2.7%) in each age group. To achieve the optimal module division, we adopted a two-step procedure, similar to the one applied by Rubinov and Sporns (2011). An initial partition into modules was created using the algorithm by Blondel et al. (2008), which attempts to maximize within module connections and minimize between module connections. As the approach is susceptible to the occurrence of local maxima, this procedure was repeated 500 times. Subsequently, all of these partitions were refined, using a modularity fine-tuning algorithm (Sun et al., 2009) which randomly assigns nodes to different modules or randomly creates a separate module. Changes that led to an increase in modularity were retained. The fine-tuning algorithm was applied repeatedly until the modularity of the partitioning no longer increased, and the partitioning with the highest modularity was used for further analyses.

To compare the module decompositions in older and younger participants, we used normalized mutual information (NMI). NMI measures how much information is provided by one set of assignments about another set of assignments (Strehl & Ghosh, 2003) and varies from 0 (no mutual information) to 1 (identical node assignments). Statistics on differences in module decomposition between age groups (NMI smaller than 1) was obtained using permutation testing. In the permutation procedure, participants were randomly divided into two groups (retaining original group sizes). Subsequently, the optimal module decomposition was calculated for each group and their NMI was calculated as described above. This procedure was repeated 1000 times to get a distribution of NMI values under

the null hypotheses. If the actual NMI between age groups was smaller than the 5th percentile of this distribution, the difference between groups was considered significant.

To find modules which were representative for both the older and the younger participants, we used the intersection of the modules defined in the two groups. Only nodes that belonged to a specific module in both groups, were taken as representative of that module for both groups. Additional details on how common networks were constructed are reported in the results section. For each of the five large networks defined in this manner, we computed the average local efficiency and participation coefficient. The participation coefficient is an index of the number of between module connections versus the total number of connections of a certain node (Guimerà & Amaral, 2005).

To examine the connectivity within and between all the different modules we developed a specific procedure, which was performed separately for both negative and positive connections. For this analysis the original weighted graph was used. Correlations with  $p < 0.05$  after false discovery rate correction (FDR, Benjamini & Hochberg, 1995) were retained, while all other correlations were set to zero. For each pair of modules and within each module, we then computed the sum of all correlations and divided these by the number of possible correlations. Group comparisons were performed with Mann Whitney U tests.

### 3.3.6 Correlation with behavioral measures

To assess how the observed changes in network properties affected the functioning of older participants, the relation with cognitive performance was examined. All participants were tested on an extensive neuropsychological battery, consisting of visual-motor sequencing (Trail making test A and B, Reitan, 1958; Tombaugh, 2004), executive functioning (Stroop task, Stroop, 1935), working memory and incidental recall (digit span test forward and backward, Wechsler Intelligence Scale - Revised, Wechsler, 1981), verbal learning (Dutch version of the Rey Auditory Verbal Learning Test, Lezak et al., 2004), and a simple reaction time test. In addition, an estimation of crystallized intelligence (Dutch version of the National Adult Reading Test, Schmandt et al., 1992) and fluid intelligence (matrix reasoning test, Wechsler Intelligence Scale - Revised, Wechsler, 1981) was obtained. One younger participant was excluded from the analysis because neuropsychological data was not available. All neuropsychological test scores were transformed to z-scores and scaled such that a higher value indicates better performance. Because some of the neuropsychological test scores were highly correlated, we first performed factor analysis on the neuropsychological tests using maximum likelihood estimation and varimax rotation. Four factors, with an eigenvalue above 1, were chosen based on the interpretability of the results. Subsequent correlations with complex network measures were performed using participant factor scores. Only complex network measures that showed a significant

difference between the age groups were related to behavioral performance.

### 3.3.7 Correlation with structural measures

To assess whether complex network measure differences between younger and older adults were related systematic gray matter volume differences between the groups, the determinant of the Jacobian matrix was used. This determinant is the local expansion factor, which results from the DARTEL procedure and represents differences in local volume between the individual images and the template brain. Values of the Jacobian determinant that are larger than 1, indicate volume expansion relative to the group template, whereas values smaller than 1 indicate contraction (Lee et al., 2007). For each functional area that was used in the graph analysis, the corresponding average Jacobian determinant was extracted for each participant. Subsequently, Spearman rank correlations were computed between complex networks measures and the Jacobian, both averaged across all functional areas as well as for each module separately.

## 3.4 Results

### 3.4.1 Functional networks in old and young

Functional networks were identified separately in the older and the younger group, by using module decomposition algorithms (Rubinov & Sporns, 2011). The modules we identified were similar to the functional brain networks described in the literature (Damoiseaux et al., 2006) and to the modules described by Power and colleagues (Power et al., 2011) (see figure 3.1A). To examine the similarities between the node-module assignments (i.e. which nodes are assigned to which functional networks) of older adults and younger adults, we used normalized mutual information (NMI). Subsequently, permutation testing was used to test whether this similarity was significantly below chance level. Over all nodes and all modules, the NMI between older and younger participants was 0.6, which was significantly lower than expected by chance ( $p=0.006$ ). Tests per module revealed significant differences between younger and older participants in the visual module ( $NMI=0.63$ ,  $p=0.001$ ), whereas no significant differences between age groups were observed in the somatomotor and cingulo-opercular network ( $NMI=0.66$ ,  $p=0.07$  and  $NMI=0.60$ ,  $p=0.69$ , respectively). In addition, age-related differences were observed in the fronto-parietal control network (FPCN) and the default mode network (DMN). While the FPCN and the DMN were separate modules in younger participants, they were identified as one module in the older participants. The NMI expressing the extent to which DMN/FPCN node assignment in the older group was predicted by node assignments of both the DMN and the FPCN in the younger group was 0.39. This similarity

was significantly below chance level ( $p=0.009$ ). The null distributions of the permutation tests per module are shown in supplementary figure 3.6. To test whether the observed age-differences are specific to the threshold of 2.7% applied here, we repeated the analysis presented above for a range of thresholds between 2% and 10%. At all of the thresholds, a significant difference in module decomposition between younger and older participants was observed (see figure 3.3B).

To compare characteristics of networks between the younger and older groups, we first derived common networks. The nodes belonging to the same network in both groups were taken as representatives of that network (see figure 3.1C and table 3.1). The DMN and FPCN modules were based on the node assignments in young participants but included only nodes that belonged to the DMN/FPCN in older participants. In figure 3.1B, the average graphs of the younger and older participants are presented using a force atlas layout. To illustrate age-related differences in labeling, the graphs of older and younger participants are presented both with the labeling of their own group and with the labeling of the other group.

### 3.4.2 Age-related changes in network distinctiveness: modularity and participation coefficient

Segregation of functional networks was reduced in the older (mean modularity old ( $M_{old}$ ) =0.61) compared to the younger participants ( $M_{young}$  =0.67;  $z=5.3$ ,  $p<0.001$ ), see figure 3.2A. Additional correlation analyses between modularity and age within the older group revealed no significant correlation ( $r=-0.21$ ,  $p=0.22$ ). The difference between the age groups can also be observed in figure 3.1B; nodes within functional networks are less clustered in older than in younger participants. Particularly, the visual network shows more pronounced local isolation in younger than in older participants. Confirming these findings, the participation coefficient was increased in older compared to younger participants in the visual and the somatomotor networks ( $z=4.53$ ,  $p<0.001$ ;  $z=4.04$ ,  $p<0.001$ , respectively), indicating that a larger proportion of the connections of the nodes in these networks are directed to nodes outside the network (see figure 3.2B). Similar to Power and colleagues (Power et al., 2011), we observed that the FPCN was the network with the highest proportion of inter-network connections (the highest participation coefficient). This is in agreement with its central role in cognitive control, requiring communication with other networks (Spreng et al., 2010; Vincent et al., 2008).

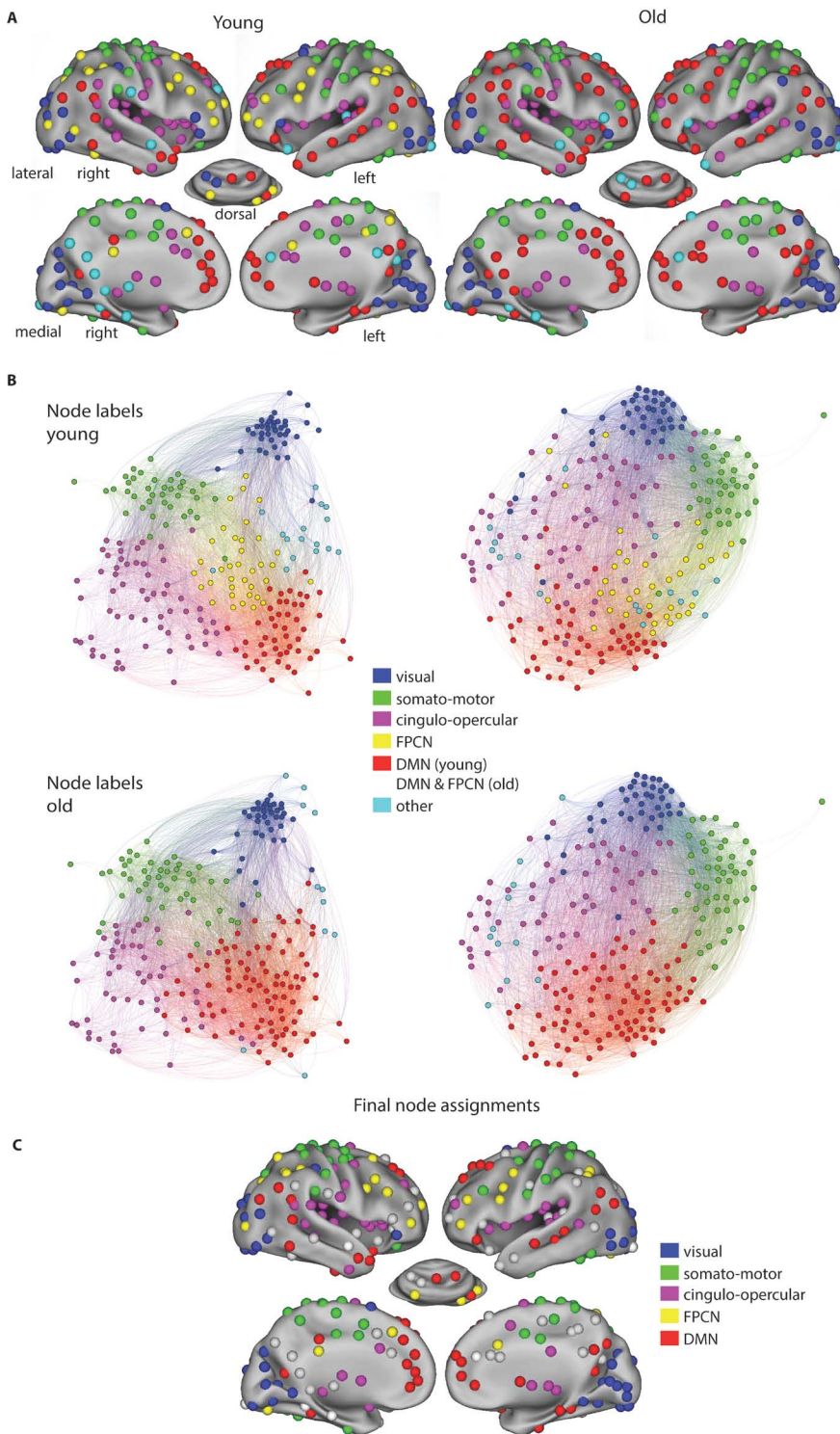


Figure 3.1: **A** The different modules are shown separately for older (right) and younger (left) participants. The colors indicate the nodes that belong to each module. Nodes are pasted on an inflated surface rendering of the human brain using the CARET program (Van Essen et al. 2001). **B** The graphs for younger (left) and older (right) participants are visualized using a force atlas layout implemented in Gephi (Bastian, Heymann, Jacomy 2009). The top row shows the graphs of younger and older participants with the node assignments of the younger participants. The bottom row shows the graphs for both groups with the node assignments of the older participants. **C** Final node module assignments based on the intersection of node assignments in both groups. Grey nodes were not assigned to any of the modules.



Table 3.1: Nodes assigned to each module in younger and older participants: overlap and differences

		Young						Total (count)	% nodes in common
		Visual	Somato-motor	Cingulo-opercular	DMN	FPCN	Other		
Old	Visual	33	0	0	4	0	1	38	87%
	Somato-motor	0	37	3	6	0	1	47	79%
	Cingulo-opercular	0	0	47	0	2	1	50	94%
	DMN & FPCN	1	1	9	26	44	8	89	79%
	Other	4	0	0	0	2	5	11	
	Total (count)	38	38	59	36	48	16	235	
	% nodes in common	87%	97%	80%	72%	92%			

Total (count) refers to the number of nodes in each module. % nodes in common refers to the percentage of nodes assigned to a specific module that ended up in the same module in the final node-module assignments.

### 3.4.3 Age-related changes in efficiency of connectivity: global and local efficiency

While global efficiency was similar in older and younger participants ( $M_{\text{young}}=0.20$ ,  $M_{\text{old}}=0.20$ ,  $z=0.25$ ,  $p=0.80$ ), local efficiency was significantly reduced in the older compared to the younger participants ( $M_{\text{young}}=0.35$ ,  $M_{\text{old}}=0.39$ ,  $z=4.7$ ,  $p<0.001$ ). These results were independent of the chosen connectivity threshold (see Figure 3.3). Separate analyses in each functional network showed an age-related decrease in local efficiency in the DMN ( $z=2.87$ ,  $p=0.004$ ), the FPCN ( $z=2.51$ ,  $p=0.012$ ) and the cingulo-opercular network ( $z=3.53$ ,  $p<0.001$ , see figure 3.2B). Correlations between local or global efficiency and age within the older group, did not show any significant effects ( $r=0.22$ ,  $p=0.20$ ;  $r=0.05$ ,  $p=0.78$ , respectively). Additional analyses with more stringent movement correction criteria (0.3 mm) and additional low pass filtering (0.08 Hz) did not change the effects of age group on the network measures described above (global and local efficiency, modularity and participation coefficient, see supplementary figures 3.3 and 3.4). As a final check, we investigated the effect of global signal regression on the results. In the literature, it has been shown that global signal regression can have both positive and negative effects on the analysis of functional connectivity (Murphy et al., 2009; Song et al., 2012; Weissenbacher et al., 2009). Therefore, we have repeated the analyses without global signal regression. Although these analyses point to the same pattern of differences between older and younger participants, some differences were observed compared to

the original analyses. These are presented and discussed in the supplementary materials (see supplementary figure 3.5).

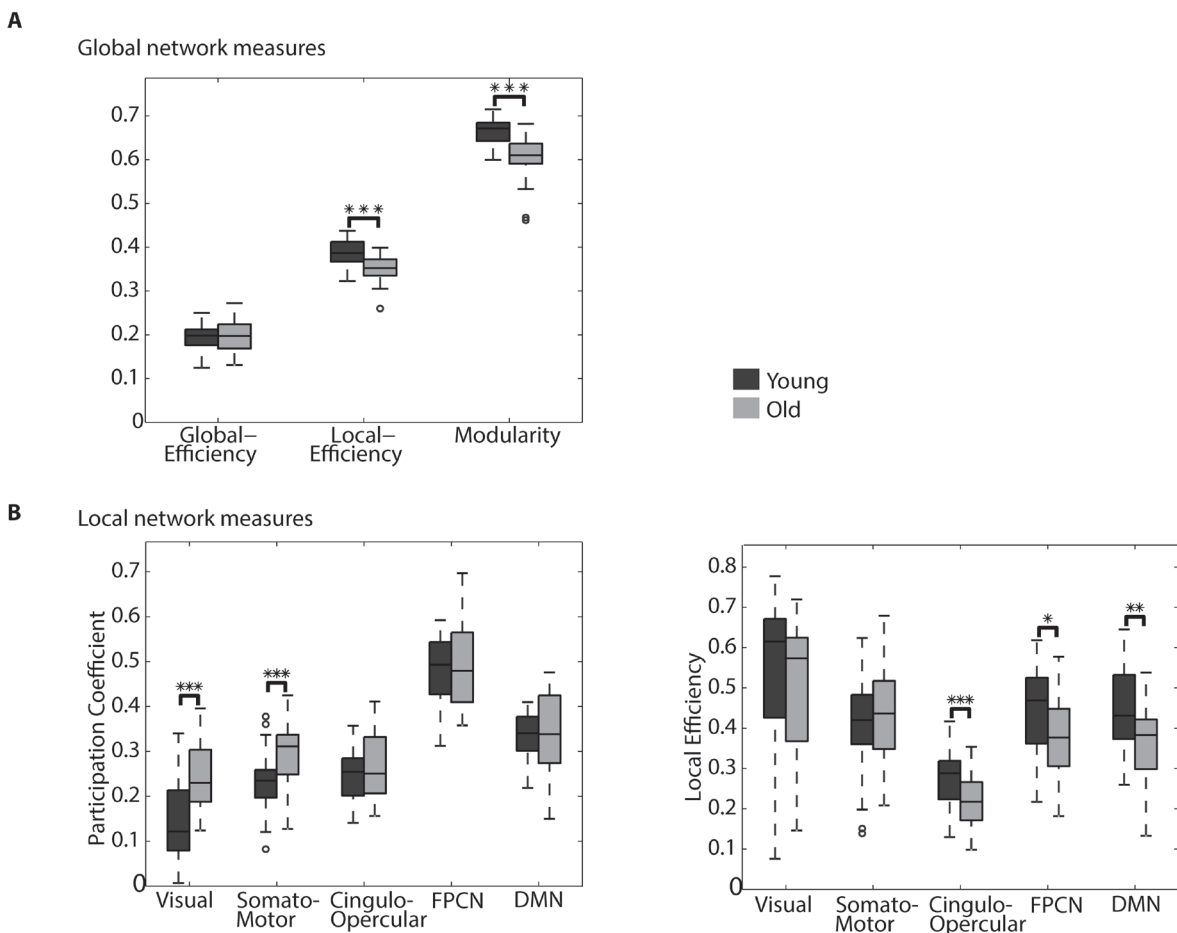


Figure 3.2 : **A** Global network measures are presented in boxplots for older (lighter) and younger (darker) participants. From left to right, global efficiency, local efficiency and modularity. Stars indicate a significant difference between the older and younger participants ( $***p < 0.001$ ). **B** For each of the functional networks (modules), participation coefficient and local efficiency are displayed in boxplots for younger and older participants. The darker boxplots represent the younger participants, the lighter boxplots the older participants. Difference between the older and younger groups;  $*p < 0.05$ ,  $**p < 0.005$ ,  $***p < 0.001$ .

#### 3.4.4 Age-related changes in functional connectivity within and between networks

Functional connectivity is reflected in the strength of the correlations between all functional brain areas. To examine the effect of age on overall functional connectivity, we compared the correlation distribution of the unthresholded correlation matrix between younger and older participants. The number of negative correlations (between -0.25 and -0.15) and the number of strong positive correlations (between 0.4 and 0.8) was reduced in elderly ( $p < 0.05$ , see figure 3.4A).



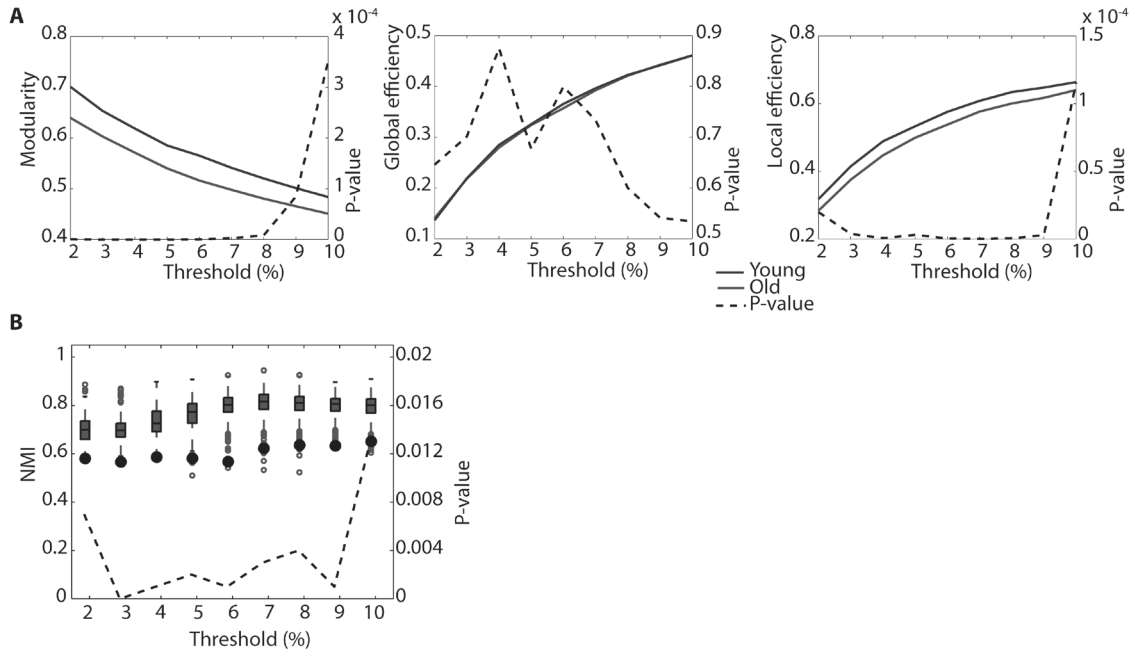


Figure 3.3: **A** Differences between old and young participants in modularity, global efficiency and local efficiency are plotted for thresholds between 2 and 10% of all possible connections. The dashed line indicates the p-values corresponding to the difference between the two groups, these values are presented on the right y-axis. **B** A test of age-related differences in module decomposition is shown over a range of thresholds. The null distribution of NMI values resulting from the permutation testing procedure is shown in the boxplots. The black dot represents the actual NMI value of the correspondence between the two age groups.

Correlations between 0.08 and 0.18 were more pronounced in elderly. Taken together, overall functional connectivity decreased with age.

In addition, functional connectivity within and between each of the functional networks was examined. To distinguish effects of aging on positive and negative correlations (also referred to as anti-correlations Fox et al., 2009), these were examined separately (see figure 3.4B). The strength and number of correlations was combined in a single measure (total positive correlation or total negative correlation, respectively) and compared between younger and older participants. To select relevant connections an FDR-threshold was applied ( $p < 0.05$  FDR corrected) to the correlation matrix of each participant. Subsequently node-module assignments were used to identify correlations within and between specific networks. The connectivity within the cingulo-opercular control network ( $z = 4.59$ ,  $p < 0.001$ ), the FPCN ( $z = 2.64$ ,  $p = 0.008$ ) and the DMN ( $z = 4.23$ ,  $p < 0.001$ ) was reduced with age, as was the connectivity between the cingulo-opercular network and the somatomotor network ( $z = 2.02$ ,  $p = 0.04$ ). The connectivity between the visual network and the somatomotor networks ( $z = 3.04$ ,  $p = 0.002$ ) and between the visual and the cingulo-opercular network ( $z = 2.62$ ,  $p = 0.009$ ) increased with age.

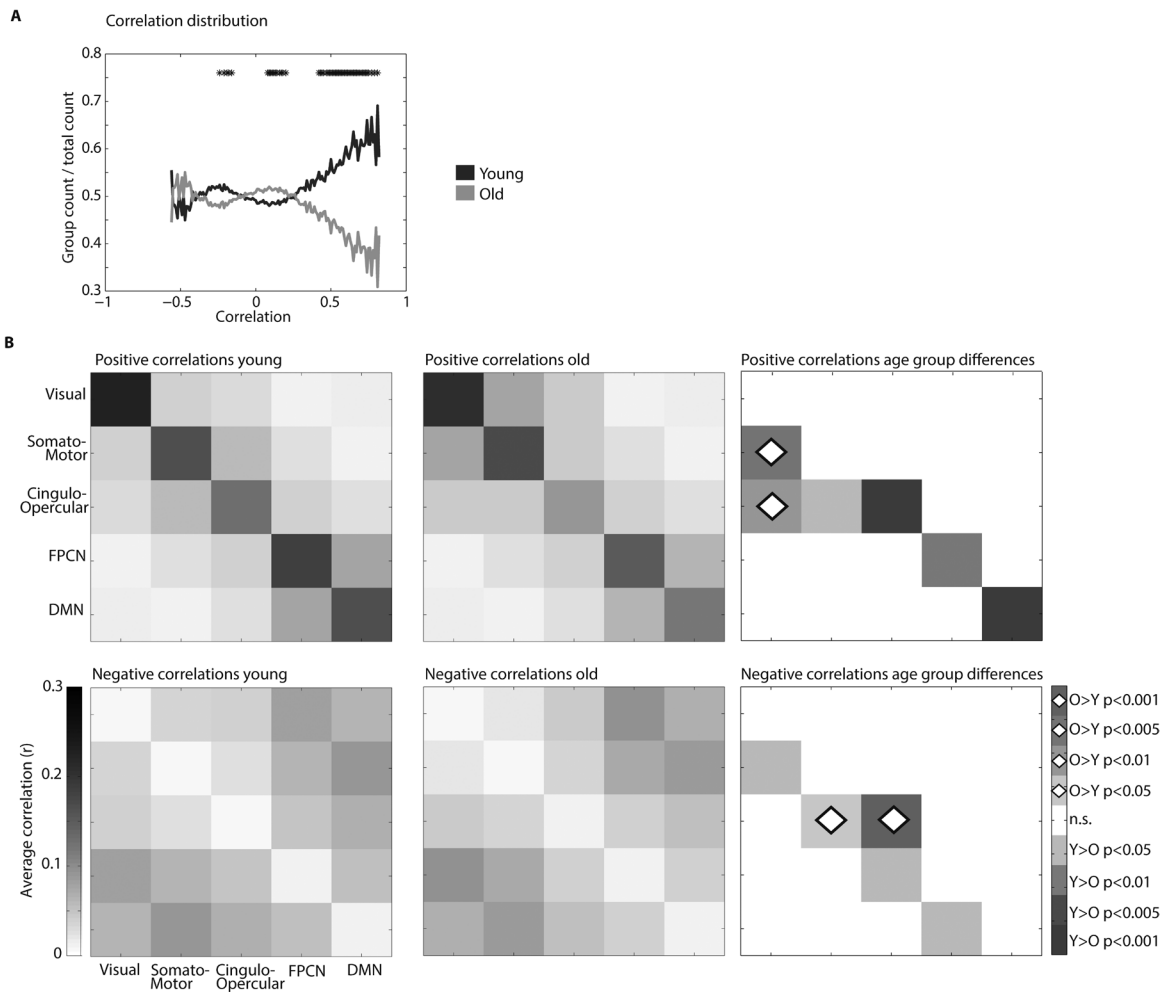


Figure 3.4: **A** The distribution of correlations shown for older (lighter) and younger (darker) participants. The number of correlations was counted in the separate bins with a size of 0.01. On the y-axis, the average number of correlations within the group, divided by the average number of correlations across both groups is depicted. A bin was included if at least half of the participants had one or more correlations in that particular bin. Stars indicate bins showing a significant difference between older and younger participants ( $*p<0.05$ ). **B** Average total functional connectivity (representing both strength and number of correlations) within and between networks is shown for younger (left) and older (middle) participants. The upper row demonstrates the changes in positive correlations, whereas the bottom row demonstrates the changes in negative correlations. The right panel shows significant differences in functional connectivity between both age groups. A fully filled square indicates decreased total correlations with age, a filled square with a diamond shape indicates increased total correlations with age.

Negative correlations were reduced in elderly between the somatomotor network and the visual network ( $z=2.48$ ,  $p=0.013$ ), between the cingulo-opercular network and the FPCN ( $z=2.01$ ,  $p=0.044$ ) and between the DMN and the FPCN ( $z=2.07$ ,  $p=0.038$ ). An increase in negative correlations was observed between the cingulo-opercular network and the somatomotor network ( $z=2.04$ ,  $p=0.042$ ) and within the cingulo-opercular network ( $z=4.24$ ,  $p<0.001$ ).

Uddin and colleagues (2009) argued that the negative correlations between the DMN and FPCN result from a unilateral influence of the DMN on the FPCN. Therefore, we tested whether decreased intra-network connectivity in either the FPCN or DMN was indeed related to a decrease in negative correlations between the DMN and FPCN. We found that correlations within the DMN were associated with negative correlations between the DMN and FPCN in both younger ( $r=0.33$ ,  $p=0.044$ ) and older participants ( $r=0.47$ ,  $p=0.005$ ). However, correlations within the FPCN were not predictive of negative correlations between the DMN and FPCN in younger ( $r=-0.01$ ,  $p=0.95$ ) nor older participants ( $r=-0.06$ ,  $p=0.72$ ).

### 3.4.5 Age-related changes in network measures related to cognitive performance

Cognitive performance was assessed by neuropsychological tests in all participants. Since some of the neuropsychological test scores showed high collinearity, we first performed factor analysis on the data of all participants (younger and older) to cluster the tests. Four factors were identified: verbal learning, loading high on the Rey auditory verbal learning test direct recall (0.77) and recognition (0.98); processing speed, with high loadings on the trail making tests A (0.84) and B (0.58), symbol substitution test (0.53) and matrix reasoning test (0.47); working memory, loading high on the forward (0.52) and backward digit span (0.95); crystallized intelligence with high loadings on the trail making B (0.45) and adult reading test (0.61). Older participants showed a significant decline of performance in verbal learning ( $z=3.36$ ,  $p<0.001$ ) and processing speed ( $z=3.22$ ,  $p=0.001$ ) but not on working memory or crystallized intelligence.

For each of the network measures that showed an effect of age, we tested whether it was related to any of the four neuropsychological test factors, using partial Spearman correlations, controlling for the effects of age. Within the younger group, we found that reduced modularity was related to better verbal learning ( $r=-0.37$ ,  $p=0.025$ ), while increased local efficiency in the full graph was related to increased processing speed ( $r=0.37$ ,  $p=0.028$ ). Modularity and local efficiency did not show significant relations with performance in the older group.

Within the younger group, we found that better verbal learning was associated with increased local efficiency and intra-network connections within the DMN ( $r=0.40$ ,  $p=0.015$  and  $r=0.40$ ,  $p=0.015$  respectively). In addition, better verbal learning was related to increased negative correlations between the cingulo-opercular network and the DMN and between the FPCN and DMN ( $r=0.39$ ,  $p=0.019$  and  $r=0.42$ ,  $p=0.01$ , respectively). Increased working memory was associated with decreased local efficiency within the cingulo-opercular network ( $r=-0.33$ ,  $p=0.044$ ) and decreased negative correlations between the cingulo-opercular network and the FPCN ( $r=-0.35$ ,  $p=0.037$ ). In elderly, increased intra-network correlations in the FPCN were related to increased working

memory ( $r=0.34$ ,  $p=0.043$ ) and crystallized intelligence ( $r=0.39$ ,  $p=0.019$ ). In addition, increased crystallized intelligence was associated with increased negative correlations within the cingulo-opercular network ( $r=-0.35$ ,  $p=0.042$ ). It should be noted that the correlations between behavior and network measures do not survive an FDR correction for multiple comparisons. Therefore, these results should be interpreted with caution.

### 3.4.6 Age-related changes in network measures related to structural differences

The Jacobian determinant was used as a measure of local gray matter volume differences between the individual images and the DARTEL template. In the young, the Jacobian determinant (local expansion factor) tended to be larger (1.058) than in the older participants (0.978;  $z=1.72$ ,  $p=0.085$ ), indicating that on average, the local volume was larger in younger than older participants. The same pattern was observed in all five separate modules (visual,  $z=3.09$ ,  $p=0.002$ ; somatomotor,  $z=1.92$ ,  $p=0.055$ ; cingulo-opercular,  $z=2.99$ ,  $p=0.003$ ; FPCN,  $z=3.99$ ,  $p<0.001$ , DMN,  $z=4.84$ ,  $p<0.001$ ).

We found that the average Jacobian determinant over the whole brain correlated significantly with the whole brain local efficiency ( $r=0.31$ ,  $p=0.006$ ) as well as modularity ( $r=0.32$ ,  $p=0.005$ ) but not with the global efficiency ( $r=0.18$ ,  $p=0.12$ ). When we examined the correlations for each specific network, we found that some of the network measures that changed with age, were correlated with the Jacobian determinant. For the local efficiency per module, we found no significant correlations with the Jacobian determinant (visual,  $r=0.14$ ,  $p=0.22$ ; somatomotor,  $r=0.04$ ,  $p=0.77$ ; cingulo-opercular,  $r=0.21$ ,  $p=0.076$ ; FPCN,  $r=0.07$ ,  $p=0.56$ ; DMN,  $r=0.16$ ,  $p=0.16$ ). For the participation coefficient, we found a significant correlation with the Jacobian determinant ( $r=-0.35$ ,  $p=0.002$ ) only in the somatomotor network. In the other networks no significant relationship was observed (visual,  $r=-0.06$ ,  $p=0.59$ ; cingulo-opercular,  $r=-0.10$ ,  $p=0.41$ ; FPCN,  $r=-0.06$ ,  $p=0.61$ , DMN,  $r=0.02$ ,  $p=0.85$ ).

## 3.5 Discussion

Using complex network measures, we identified clear differences in the organization of connections within and between functional networks with age. Brain networks in the elderly showed decreased modularity and decreased local efficiency within the DMN, FPCN and cingulo-opercular networks. Conversely, local efficiency in the visual and somatomotor networks was not affected by age while the participation coefficient of these networks was increased in elderly. Additional analyses showed that this increase in participation coefficient was due to increased connectivity between the visual and somatomotor network, as well as, between the visual and cingulo-opercular network.

In younger adults, functional brain networks were found to be highly modular, as reflected in high intra-network connectivity along with few inter-network connections (Ferrarini et al., 2009; Meunier et al., 2010). In this study we have shown that this modularity is reduced in elderly, indicating that functional brain networks become less differentiated or less specific with age. These findings are in accordance with our previous study, where we used seed based correlation analyses to demonstrate an increase in inter-network connections along with decreased intra-network connections during task performance (Geerligts et al., 2012a). The present study extended these findings in two ways. First, the current findings demonstrate that age-related changes in functional connectivity are general and not restricted to performance during specific tasks. Second, the use of graph theory allowed us to quantify the effects of age on modularity. These effects are large, there is only little overlap in the modularity values of younger and older participants (see figure 3.2A).

The dedifferentiation theory suggests that overactivation of brain areas in elderly might be due to a decrease in functional distinction between brain areas (Baltes & Lindenberger, 1997; Carp et al., 2011a; Dennis & Cabeza, 2011; Park et al., 2004). In line with our previous study (Geerligts et al., 2012a), the current findings show that dedifferentiation also occurs on the level of functional networks. Functional networks show increased inter-network connections in older age along with decreased intra-network connections, which makes them less distinct. These age-related changes in functional connectivity could be related to a dedifferentiation of activation patterns. Although the term dedifferentiation has often been used to indicate a link with age-related declines in performance, the increase in inter-network connections might also have a compensatory role.

Along with reduced modularity, the local efficiency across the whole network was reduced in elderly, while global efficiency was not affected by aging. The latter finding might be related to the increase in inter-network connections with age. Our findings are partly in accordance with previous results (Achard & Bullmore, 2007), that have shown a reduction in local efficiency and global efficiency with age, while modularity was reported to be stable across age groups (Meunier et al., 2009a). Differences between those results and the current findings may be related to the regional parcellation of the brain that was used in the previous study for graph construction (90 vs. 235 nodes in the present study), which has a limited ability to represent functional networks due to coarse nodes which encompass different functional areas (Power et al., 2011).

It has been suggested that over-activations in elderly are caused by less efficient use of neural resources (reduced cost efficiency); this theory has related over-recruitment of brain areas to less efficient performance in elderly (Morcom et al., 2007; Rypma et al., 2007; Stevens et al., 2008). The decline in local efficiency can be interpreted as a sign of reduced cost efficiency in the elderly brain, that is, with the same number of connections (cost) the efficiency is decreased. Because of the large metabolic costs of supplying

the brain with resources, minimizing these costs is likely one of the selection pressures during evolution (Chen et al., 2006). Minimal metabolic costs can be achieved through high clustering of connections in brain networks (i.e. high local efficiency) along with sparse long range connections which are more costly but greatly increase the speed of information transfer (Bullmore & Sporns, 2012; Buzsáki et al., 2004; Kitzbichler et al., 2011). Even though for older and younger participants the analyzed graphs contained the same number of connections, the local efficiency in the resulting network was smaller in the older participants. Furthermore, we found an increase in the number of inter-modular connections in older compared to younger participants. Inter-modular connections tend to be longer and therefore more costly, than intra-modular connections (Meunier et al., 2010). Together, these findings indicate a decrease in the cost efficiency of functional networks of elderly. Note that we have shown that the reduction in cost efficiency is not only present during task performance (Morcom et al., 2007; Rypma et al., 2007; Stevens et al., 2008) but also during resting state conditions.

In addition to comparisons between age groups, we also studied the correlations between the global network measures (modularity and global and local efficiency) and chronological age within the older group. No significant correlations were observed, which suggests that the changes in functional connectivity are not linearly related to chronological age. This fits with the model presented in a recent review article of Grady (2012), which illustrates how the effect of aging on functional connectivity could be mediated by many different (environmental) factors. These mediating variables (e.g., such as stress, education, exercise, genes, life experiences and diet (Kramer et al., 2004; Milgram et al., 2002; Pesonen et al., 2013)) might obscure a linear relation between aging and functional connectivity.

Besides age-related changes in global network properties, we showed changes in connectivity within and between specific functional networks in the older brain. Inter-network connections increased with age, primarily between the visual, somatomotor and cingulo-opercular networks. Local efficiency and intra-module correlations within the cingulo-opercular network, the FPCN and the DMN decreased with age. These results are in line with a recent study by Tomasi and Volkow (2012). They examined functional connectivity in relation to aging and showed that long range connectivity decreased from areas within the DMN and FPCN, while long range connectivity increased from areas in the somatomotor network, thalamus and cerebellum.

Previous research has linked age-related decreases in connectivity within the DMN to decreased memory, executive functioning and processing speed (Andrews-Hanna et al., 2007; Geerligs et al., 2012a; Sambataro et al., 2010). Decreased connectivity within the FPCN with age has also been shown before (Andrews-Hanna et al., 2007; Madden et al., 2010; Rieckmann et al., 2011) and was associated with more efficient semantic retrieval in both younger and older participants (Madden et al., 2010). In line with these findings,



we found that both connectivity within the DMN and local efficiency within the DMN correlated positively with verbal learning in younger participants. In addition, we found that connectivity changes were related to cognitive functioning; higher connectivity within the FPCN was associated with better working memory and crystallized intelligence in elderly. Although these findings are in line with the results in the literature, the correlations with behavior did not survive corrections for multiple comparisons and should therefore be interpreted with caution. Note that the decreases in intra-network connections occurred in three networks involved in higher level functions, while the networks involved in primary sensory and motor processing maintained intra-network connections with age. The findings in the literature as well as the observations in the current study suggest that the decreased connectivity within the DMN and FPCN might be related to cognitive decline in the aging brain.

The FPCN and the DMN formed one functional network in elderly in the module decomposition, while they formed separate networks in younger participants. In addition, decreased negative correlations between the FPCN and the DMN were observed with age. In several studies, it has been shown that older participants show reduced suppression of the DMN during performance of cognitive tasks (Grady et al., 2006; Lustig et al., 2003; Persson et al., 2007; Sambataro et al., 2010). In addition, the ability to flexibly decouple the FPCN from the DMN in tasks requiring an external focus was shown to be reduced with age (Spreng & Schacter, 2011). These findings were argued to reflect a decline in neuromodulation at the level of larger-scale brain networks due to deficits in executive control. The current results suggest that the reduced integrity of both the DMN and the FPCN, as well as the decreased negative correlations between the two networks, result in reduced differentiation of these two networks. This dedifferentiation might underlie the reduced ability of elderly to modulate the two networks separately during task performance.

The correlation with behavior suggests that increased negative correlations between the DMN and the FPCN in the elderly might be related to improved verbal learning. This is in agreement with previous studies that have shown an association between negative correlations between FPCN and DMN and better working memory and flanker task performance in younger participants (Hampson et al., 2010; Kelly et al., 2008). It has been suggested that the negative correlations between the DMN and FPCN are due to a unilateral influence of the DMN on the FPCN (Uddin et al., 2009). Supporting this idea, we have shown in the present study that the negative correlations between DMN and FPCN are related to the connectivity strength within the DMN but not to the connectivity strength within the FPCN, in older as well as younger participants. As aging is related to a decrease in intra-DMN connectivity as well as a decrease in DMN-FPCN negative correlations, the current findings suggest that both phenomena might be related to the reduction in intra-DMN connectivity.



### 3.5.1 Limitations

We found some interesting relations between performance on neuropsychological tests and complex network measures. Whereas some of the results are well in line with previous literature, suggesting that decreased connectivity within functional networks is related to reduced levels of task performance, for other results the interpretation is less straightforward. It is important to note that correlations between cognitive performance and network measures did not survive correction for multiple comparisons, therefore, they should be interpreted with caution to avoid speculation. However, they do provide a starting point for future studies.

Possibly, older and younger participants had different levels of arousal during the scanning session. However, there are a number of reasons why it is unlikely that such differences were the cause of the age-related effects on functional connectivity we observed. First of all, none of the participants mentioned that they had fallen asleep during the debriefing. Second, previous studies, that have examined functional connectivity differences in awake versus sleeping participants, showed only minor changes in functional connectivity (Horovitz et al., 2008; Larson-Prior et al., 2009). Furthermore, these changes were very different from the effects of aging that we observed in the current study (i.e. only a small increase in connectivity was observed during sleep within the DAN and no change was observed in the DMN in Larson-Prior et al. 2009).

In addition to functional changes, aging is known to be related to changes in underlying brain structure (Park & Reuter-Lorenz, 2009). The functional networks in which we identified an age-related decrease in local efficiency in the present study show overlap with areas that generally show age-related reductions in grey or white matter. Reduced white matter is generally observed in frontal areas of the aging brain, whereas gray matter reductions are mainly found in frontal and parietal cortices, as well as in the insula and hippocampus (Good et al., 2001; Gunning-Dixon et al., 2009; Madden et al., 2009; Raz et al., 2005; Resnick et al., 2003). We therefore performed additional analyses to examine the relation between complex network measures and structural differences. The observed correlations between whole brain local efficiency and modularity with the Jacobian determinant indicated that for these measures, it was not possible to disentangle the effects of aging on structural differences from the effects on functional connectivity. However, for the measures of local efficiency per module, we found no significant correlation with the Jacobian determinant. In addition, only for the somatomotor network, but not for the visual network, we observed a significant correlation between the Jacobian determinant and the participation coefficient. These results demonstrate that not all of the observed differences in complex network measures can be attributed to age-related differences in brain structure. This is in line with the results of a previous study (Geerligts et al., 2012a), in which we showed that changes in functional connectivity cannot be fully explained by changes in gray matter volume. Nevertheless, based on the results of the present study,

it is difficult to conclude whether the reduction of gray matter in specific functional areas (nodes) and/or the reduced white matter integrity between functional areas (edges) is an underlying cause of the decline in intra-network connections. It would be important for future longitudinal studies to assess to what extent the changes in functional connectivity are indeed driven by the changes in gray and white matter.

### 3.5.2 Conclusions

In the current study we have shown that aging has pronounced effects on specific functional networks in the brain. In general, modularity and local efficiency were reduced and the distinction between the DMN and FPCN was diminished. Moreover, we have shown that the decreases in intra-network connections did not occur in primary processing networks, but were restricted to networks involved in higher order cognitive processes. Together with the increase in connectivity between visual and somatomotor networks, these results suggest a shift in the balance between intra- and inter-network connections. The results demonstrate that a brain-wide analysis approach of functional connectivity in the aging brain is fundamental to understand how age affects integration of information, both within and between networks.

## 3.6 Supplementary material: graph thresholding

### 3.6.1 Introduction

Thesholding is generally required for graph theoretical analyses of connectivity matrices to enhance the contrast between relevant (strong) and irrelevant (weak) connectivity values (van Wijk et al., 2010). The success of this approach is dependent on the selection of an appropriate threshold. Here, we present a method to select the optimal number of edges ( $k$ ) in each subjects graph based on the stability of the presence of this edge across subjects. First we present the details of the method and then we investigate its behavior using simulations.

### 3.6.2 Method

Let  $n$  be the number of nodes within a network and  $c$  the maximum number of undirected edges between the nodes. Let  $s$  be the total number of subjects. Let  $\mathbf{Q}$  be an  $s$  by  $c$  matrix defining the strength (e.g. based on correlation of temporal behavior) of all possible edges per subject. Let  $\mathbf{B}^k$  be the binarized version of  $\mathbf{Q}$ , where the  $k$  strongest edges per subject are set to 1 and all others are set to 0. Now let  $\mathbf{F}^k$  be a 1 by  $c$  matrix,

where the  $i^{\text{th}}$  element of  $\mathbf{F}^k (f_i^k)$  is the number of subjects for which the  $i^{\text{th}}$  edge was among the  $k$  strongest. For each possible value  $j$  (1 to  $s$ ) in  $\mathbf{F}^k$ ,  $\mathbf{p}_j^k$  is now defined as:

$$\mathbf{p}_j^k = \sum_{i=1}^c a_i / c$$

$$\text{where } a_i = \begin{cases} 1 & \text{if } \mathbf{F}_i^k = j \\ 0 & \text{if } \mathbf{F}_i^k \neq j \end{cases}$$

$\mathbf{p}_j^k$  represents the probability that an arbitrary edge is selected  $j$  times. For this estimate to be reliable, sufficient edges have to be present.

$$\text{Now define } \mathbf{P}^k = \begin{bmatrix} \mathbf{p}_1^k \\ \vdots \\ \mathbf{p}_j^k \end{bmatrix}.$$

The entropy ( $\mathbf{H}^k$ ) contained in  $\mathbf{P}^k$  is now given by: 
$$\mathbf{H}^k = \sum_{j=0}^s -\mathbf{p}_j^k \log(\mathbf{p}_j^k)$$

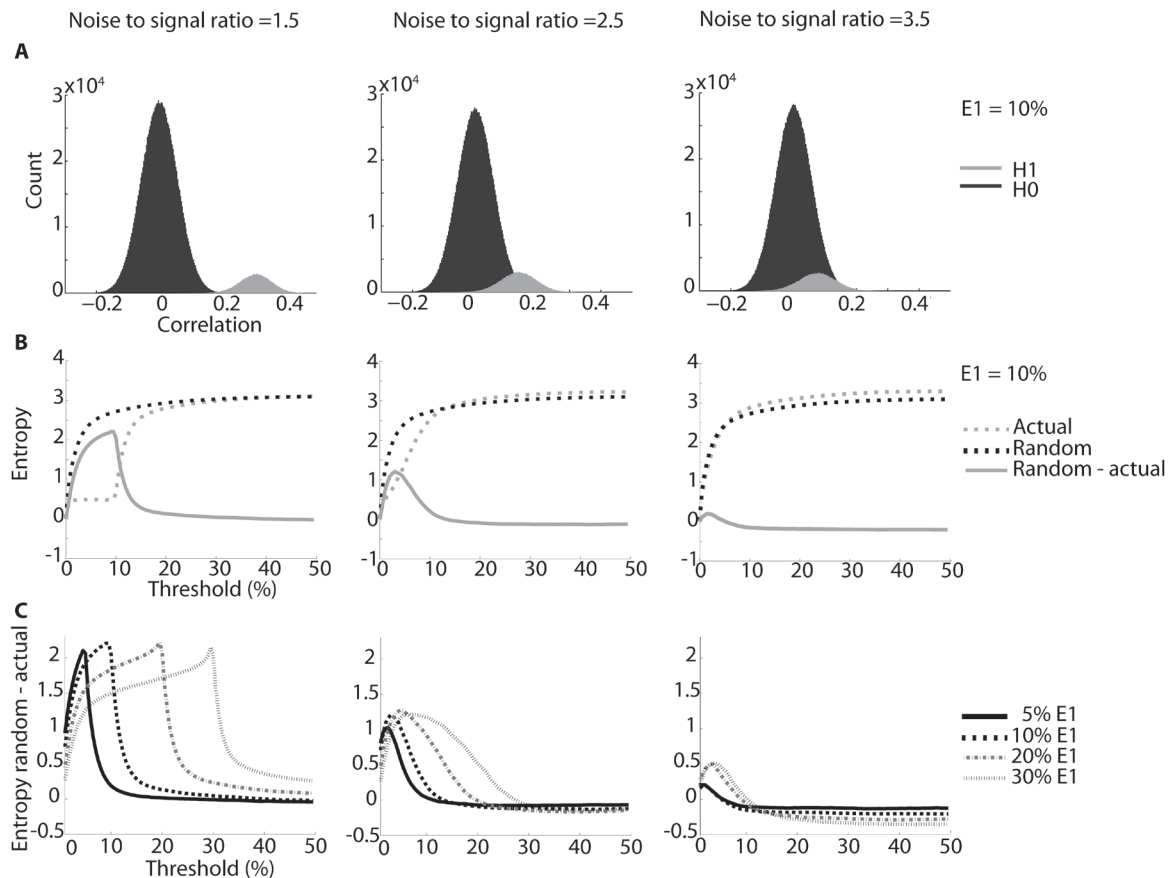
The entropy is the inverse of the information content of  $\mathbf{P}^k$  (Shannon, 1948). This value is compared against the value obtained for a random network. In a random network the chance that a specific edge is among the  $k$ -strongest for a given subject, is equal for all edges. Randomized networks were derived from  $\mathbf{B}^k$  retaining the degree distribution over nodes (Maslov & Sneppen, 2002). For this random network, a value  $\mathbf{H}_r$  can be calculated as above, where the subscript  $r$  signifies the random network. An optimal value of  $k$  would be the one where the information gain from  $\mathbf{H}_r$  to  $\mathbf{H}$  is maximal.

### 3.6.3 Simulation

To evaluate the above method, a series of simulations using surrogate data was performed. The strength of an edge was simulated as the correlation coefficient between the two time courses belonging to the nodes it connects. In all simulations it was assumed that across all subjects, an edge is either relevant (E1) or irrelevant (E0), that is, the correlation is 1 or 0, respectively, in the absence of noise. A variable amount of noise was added to the time courses to manipulate the overlap of the correlation distributions of E0 and E1 edges, with noise to signal ratios of 1.5, 2.5 and 3.5. The number of nodes was fixed at 200 and the number of subjects at 80, the number of E1-edges was set to 5, 10, 20 or 30 %.

### 3.6.4 Results and discussion

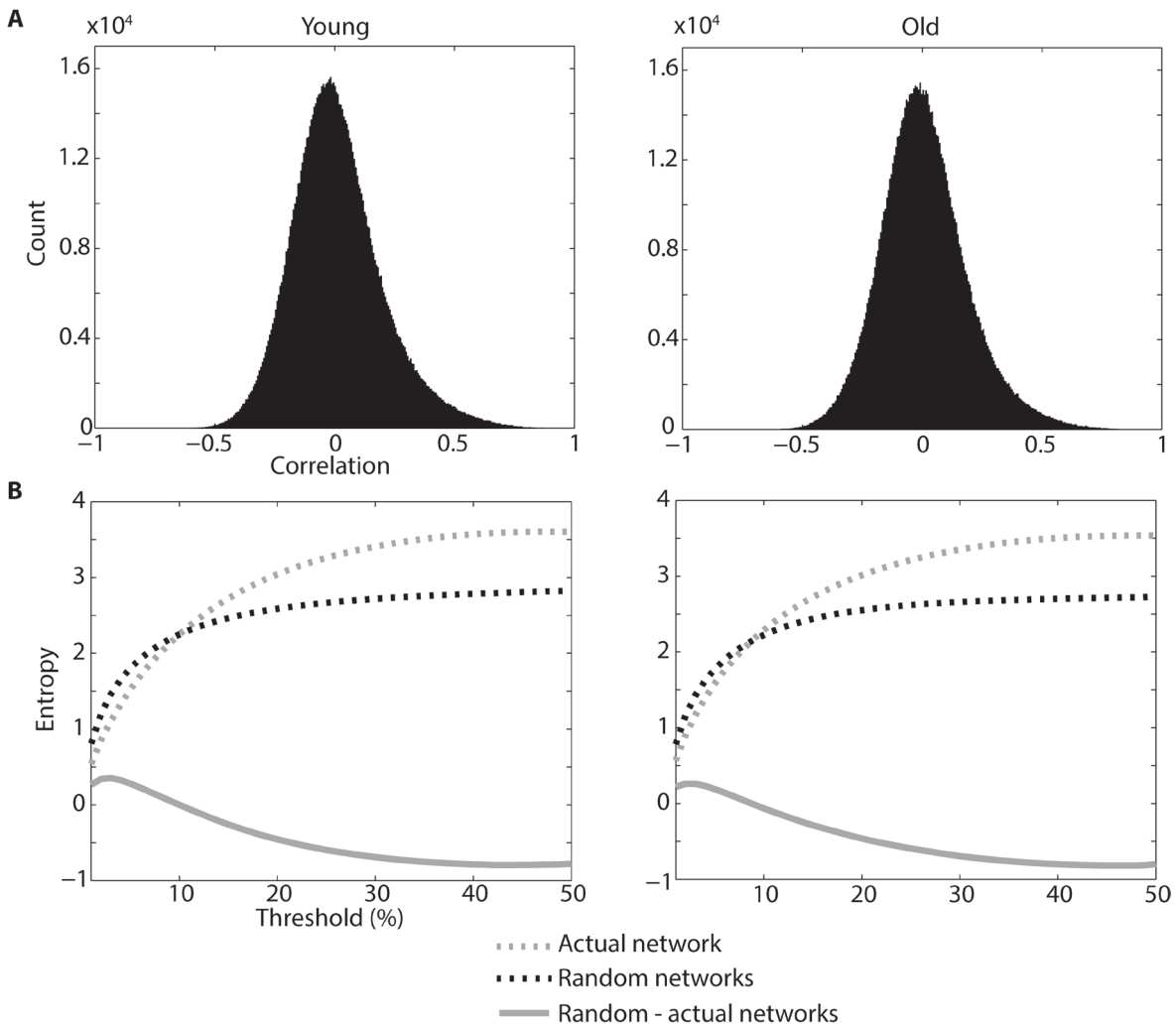
The entropy value of a matrix  $\mathbf{P}$  will depend upon the number of edges selected (at a threshold of 100% all elements will have a value of one and the entropy will be zero). Therefore, it is essential to compare the entropy of the network under investigation to the entropy of a randomized network. Comparing the information content for the actual network with a random network is intuitive.



Supplementary figure 3.1: The results of the simulation. **A** The correlation distribution of the E0 and E1 edges for varying noise to signal ratios. The number of E1 edges was fixed at 10%. **B** The dashed lines show the entropy for the actual and random networks. The solid line shows the difference between random and actual networks, for varying noise to signal ratios. Again the number of E1 edges was fixed at 10%. **C** The effect of varying the number of E1 edges on the entropy difference between random and actual networks is depicted for different noise to signal ratios.

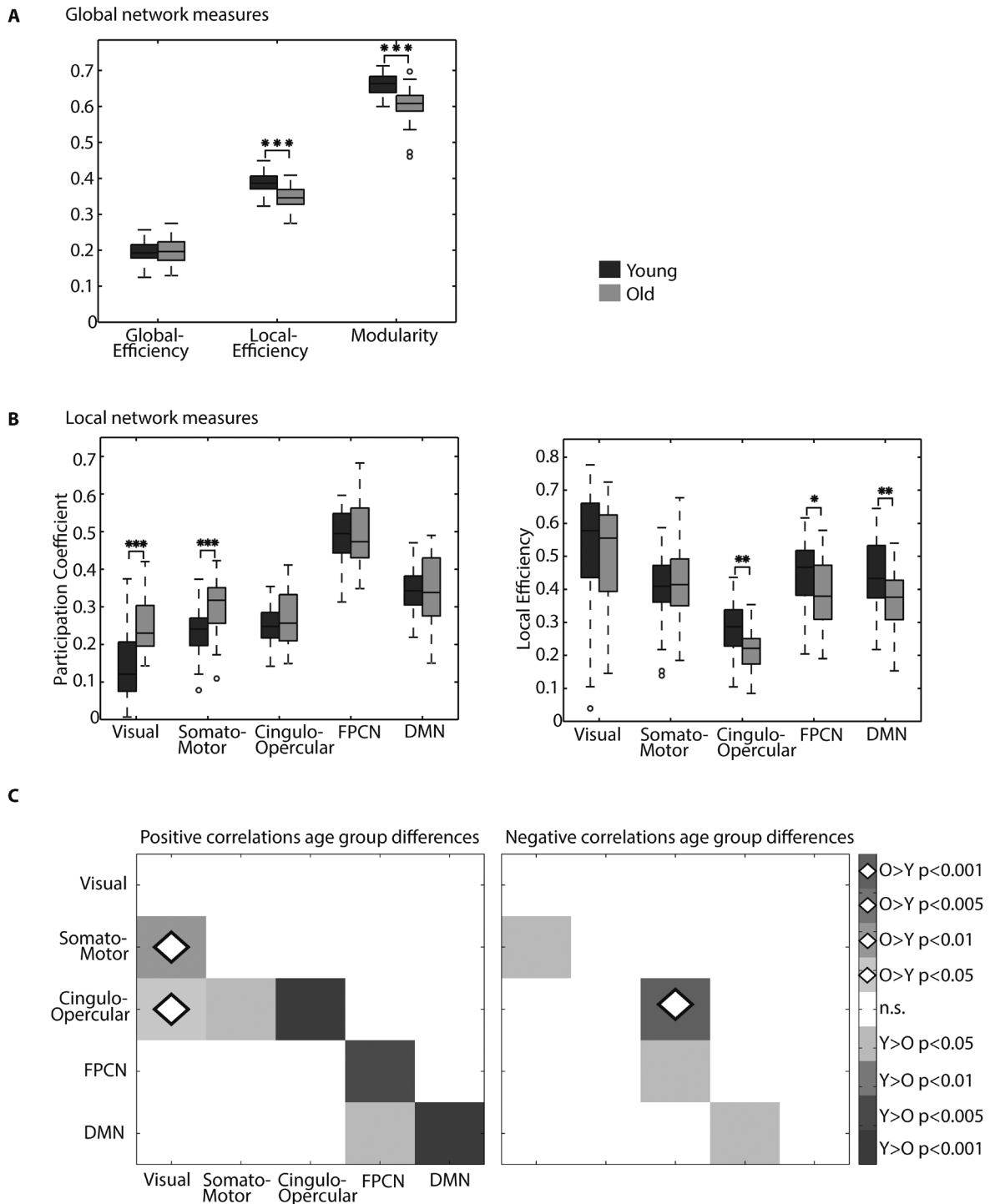
The optimal value of  $k$  is found when the information in the actual network is as unique as possible (i.e., highest stability across subjects), but more importantly, least resembles the result for a random network.

The results of the simulation (supplementary figure 3.1) demonstrate a number of properties of the current method. When the E1 and E0 distributions are perfectly separable (under low noise to signal conditions), the optimal value of  $k$  is equal to the number of E1 edges. Under these conditions, the random network shows a steady increase in entropy with increasing threshold, while the actual network only shows an increase in entropy when more edges than the total number of E1 edges are selected. As the noise increases, the optimal value of  $k$  is lower than the actual number of E1 edges. This is because the proportion of E0 edges in all selected edges increases for the actual network, given a value of  $k$ , thus resulting in less stable results across participants. Supplementary figure 3.2 demonstrates that the application of this method to the real data leads to comparable overall behavior. Furthermore, the optimal values of  $k$ , in percentages, were similar in both older and younger adults.



Supplementary figure 3.2: **A** The correlation distributions for young and older adults are shown. **B** The dashed lines show the entropy for the actual and random networks. The solid line shows the difference between random and actual networks. For older participants, the maximum difference is at 2.6%, for young participants at 2.8%.

Deriving a threshold in this way eliminates the need to try a large range of thresholds as described in previous studies (e.g. Achard & Bullmore, 2007; Van Den Heuvel et al., 2009; Zhao et al., 2012), giving more validity to the resulting statistics. In addition, we found that the use of  $P$  as the input to the module decomposition algorithm (Blondel et al., 2008) provides more stable results than using a matrix in which the edge strengths were averaged over participants (data not shown). Additional analyses for a range of thresholds, show that the chosen threshold is indeed within the range for stable results using global efficiency, local efficiency and modularity (figure 3.3). However, it should be noted that the chosen threshold was designed to be optimal for characterizing the network on a level of the group, not necessarily for the individual subject.



Supplementary figure 3.3: Age differences in complex network measures after more stringent corrections for motion (cutoff 0.3 mm instead of 0.5 mm). **A** Global network measures are presented in boxplots for older (lighter) and younger (darker) participants. From left to right, global efficiency, local efficiency and modularity. Stars indicate a significant difference between the older and younger participants (\*\*\* $p < 0.001$ ). **B** For each of the functional networks (modules), participation coefficient and local efficiency are displayed in boxplots for younger and older participants. The darker boxplots represent the younger participants, the lighter boxplots the older participants. Difference between the older and younger groups, \* $p < 0.05$ , \*\* $p < 0.005$ , \*\*\* $p < 0.001$ . **C** Differences in average total functional connectivity between both age groups. A fully filled square indicates decreased total correlations with age, a filled square with a diamond shape indicates increased total correlations with age.

### 3.7 Supplementary material: additional analyses

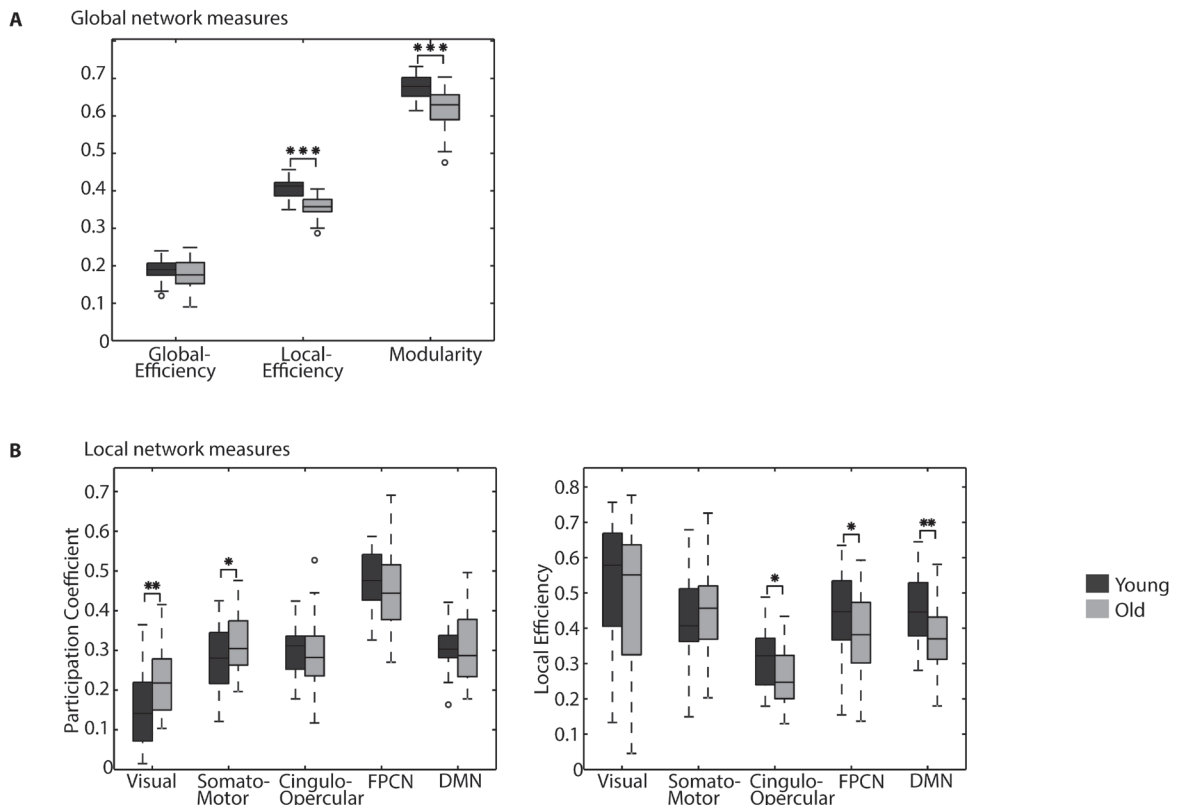
The analyses presented in figure 3.2 were repeated with a more stringent criterion for movement detection. Instead of using 0.5 mm as the cutoff, all scans with 0.3 mm or more movement were excluded in the computation of the correlation matrix. The additional criterion of a maximal intensity change of 3 standard deviations remained the same as in the previous analysis. The new criteria led to the removal of 16% of all scans on average for the younger participants and 20.7% of all scans in the older group.

The overall differences between age groups in module decomposition remained the same after this analysis (NMI=0.63,  $p=0.021$ ). There were significant differences between groups in the visual and the combined DMN and FPCN modules (NMI=0.66,  $p=0.01$  and NMI=0.39,  $p=0.005$ , respectively), whereas no significant differences were observed in the somatomotor and the cingulo-opercular modules (NMI=0.73,  $p=0.26$  and NMI=0.65,  $p=0.65$ , respectively). Results of the analysis of complex network measures as well as analysis of connectivity within and between networks are shown in supplementary figure 3.3. The effects of age group on all complex network measures remained the same regardless of the strictness of the motion detection criterion. The analysis of within and between network total correlations also gave highly similar results after the additional motion correction. The difference between the two analyses was that the age-related increase in negative connectivity between the somato-motor and the cingulo-opercular network was reduced to a trend effect ( $z=1.91$   $p=0.056$ ) and that we now observe an age-related decrease in positive connectivity between the FPCN and the DMN ( $z=2.13$ ,  $p=0.03$ ).

Correlations between behavioral measures and networks measures also remained highly similar. There were two exceptions in the younger group: the negative correlation between local efficiency in the cingulo-opercular network and working memory ( $r=-0.28$ ,  $p=0.10$ ) was no longer significant, nor was the positive correlation between verbal learning and overall connectivity within the DMN ( $r=0.31$ ,  $p=0.06$ ). In the older group, the correlation between working memory and connectivity within the FPCN was now just above the level of significance ( $r=0.33$ ,  $p=0.051$ ), just like the relation between negative connectivity in the cingulo-opercular network and crystallized intelligence ( $r=0.33$ ,  $p=0.051$ ). Note that also after additional motion correction, the correlations between behavioral measures and network measures do not survive correction for multiple comparisons.

In addition, to ensure that changes in high frequency noise between the two age groups did not influence the results, the analyses were repeated after low pass filtering of the ROI time courses. A zero-phase shift Butterworth filter was applied with a cut-off of 0.08 Hz and a filter order of 15. Due to the filter lag, the first and last 15 time points in the data were discarded in the correlation analysis.





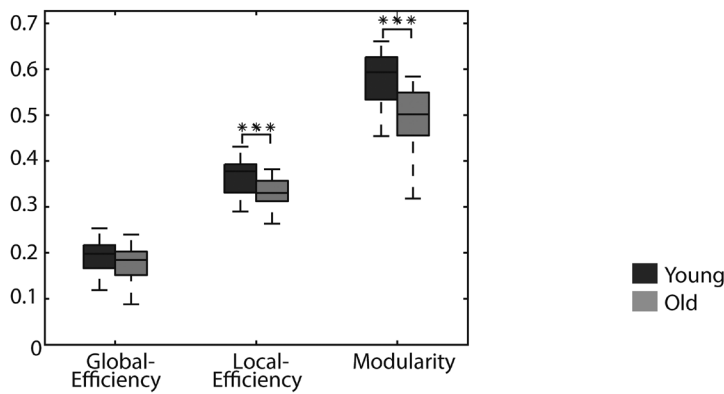
Supplementary figure 3.4: Age differences in complex network measures after additional low-pass filtering (Butterworth filter, cut-off = 0.08 Hz, filter order = 15). **A** Global network measures are presented in boxplots for older (lighter) and younger (darker) participants. From left to right: global efficiency, local efficiency and modularity. Stars indicate a significant difference between the older and younger participants (\*\* $p < 0.001$ ). **B** For each of the functional networks (modules), participation coefficient and local efficiency are displayed in boxplots for younger and older participants. The darker boxplots represent the younger participants, the lighter boxplots the older participants. Difference between the older and younger groups; \* $p < 0.05$ , \*\* $p < 0.005$ , \*\*\* $p < 0.001$ .

The results of this analysis are shown in supplementary figure 3.4 and demonstrate that the effect of age on complex network measures was not affected by low pass filtering.

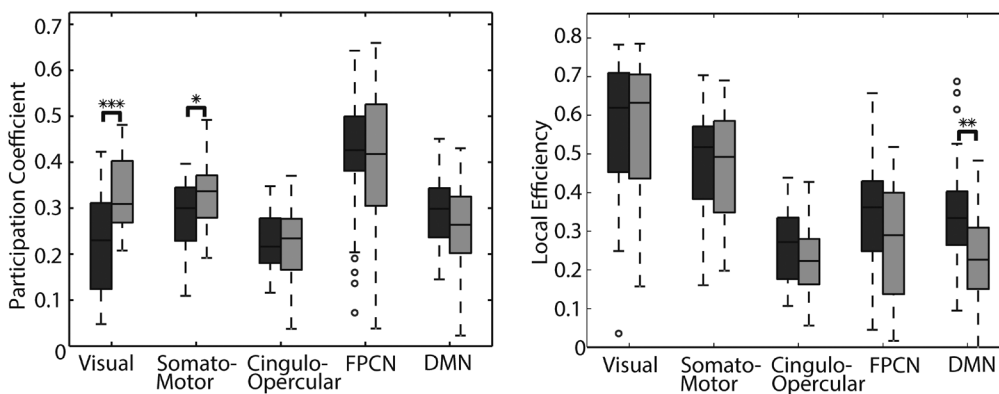
As a final check, we investigated the effect of global signal regression on the results. In literature, the use of global signal regression has been debated. On the positive side, studies have shown that global signal regression can improve the local specificity of correlations (Weissenbacher et al., 2009), reducing correlations with a non-neural origin. In addition, the stability of the functional connectivity across scans was found to increase after global signal regression (Song et al., 2012). On the other hand, it has also been shown that global signal regression might induce negative correlations that are not present prior to this correction procedure (Murphy et al., 2009; Weissenbacher et al., 2009).

The critical issue here is the presence of signal of interest in the global signal. When the global signal consists purely of physiological and non-physiological noise, global signal regression works well. However, when a substantial proportion of the global signal consists of resting state fluctuations (with a neural origin), the global signal regression

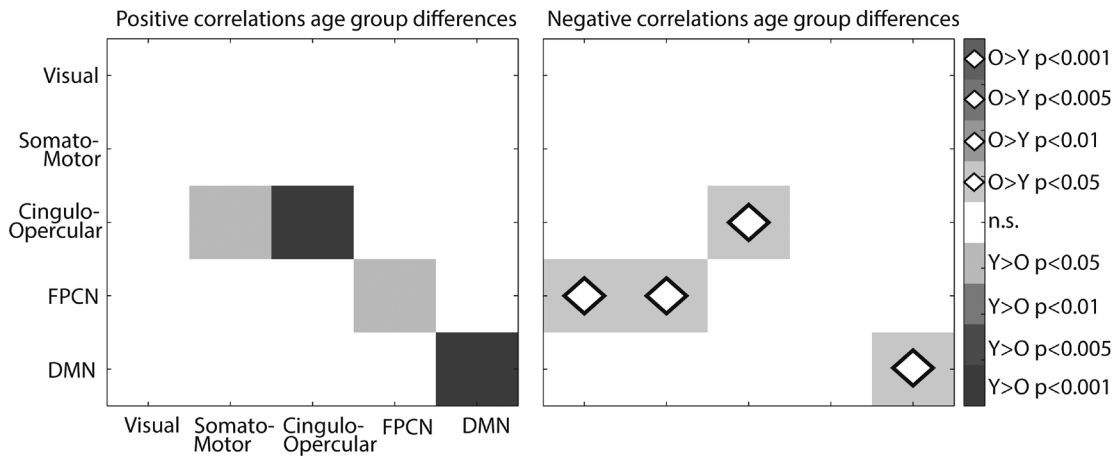
**A** Global network measures



**B** Local network measures



**C**



Supplementary figure 3.5: Age differences in complex network measures when no global signal regression is applied. **A** Global network measures are presented in boxplots for older (lighter) and younger (darker) participants. From left to right: global efficiency, local efficiency and modularity. Stars indicate a significant difference between the older and younger participants ( $***p < 0.001$ ). **B** For each of the functional networks (modules), participation coefficient and local efficiency are displayed in boxplots for younger and older participants. The darker boxplots represent the younger participants, the lighter boxplots the older participants. Differences between the older and younger groups;  $*p < 0.05$ ,  $**p < 0.005$ ,  $***p < 0.001$ . **C** Differences in average total functional connectivity between both age groups. A fully filled square indicates decreased total correlations with age, a filled square with a diamond shape indicates increased total correlations with age.

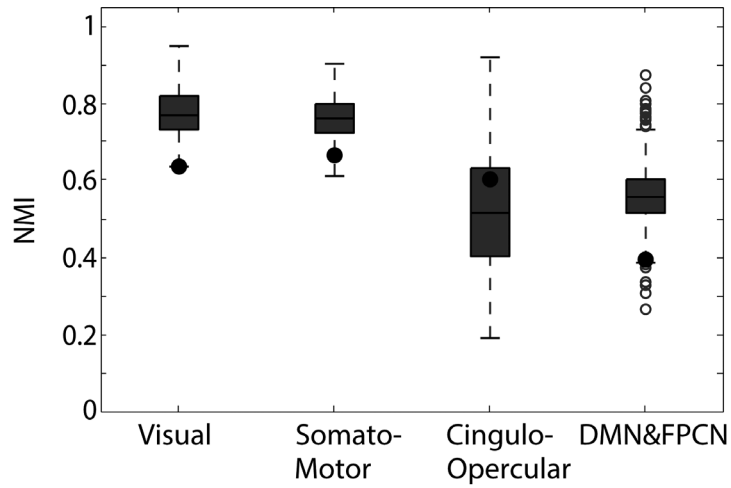
might negatively affect the results of the functional connectivity analysis (Chen et al., 2012).

To examine the influence of global signal regression in the present study, we compared the initial results with the results of additional analyses in which no global signal regression was applied. We found that the effects of aging on brain-wide network measures were the similar with and without global signal regression; older participants had reduced local efficiency and modularity (see supplementary figure 3.5A). It is important to note that the variance of the complex network measures was larger in the analysis without global signal regression, in particular for the modularity.

Whereas in the initial analysis, the results of the graph analysis corresponded very well to the analysis of total correlations, this was no longer the case after global signal regression. Similar to the original analysis, the participation coefficient indicated an increase in inter- versus intra-network connections in older adults in the visual and somato-motor networks (see supplementary figure 3.5B). However, the age-related increase in total positive connectivity between the visual and somato-motor networks was no longer significant (supplementary figure 3.5C).

For the within network connectivity we observed the same reduction of correspondence between different measures with and without the use of global signal regression. The analysis of total positive correlations still showed the significant decrease in connectivity in older adults in the DMN, the FPCN and the cingulo-opercular network. However, the local efficiency decrease in older adults was only significant in the DMN, whereas a trend was observed in the FPCN ( $z=1.87$ ,  $p=0.062$ ) and no significant difference was present in the cingulo-opercular network ( $z=1.4$ ,  $p=0.16$ ). The results with and without global signal regression thus show the same pattern of changes in the aging brain. However, without global signal regression correspondence between the difference measures was reduced.

NMI values were used to assess the similarity between module decompositions in the two age groups. To test whether the similarity was lower than expected by chance, we used a permutation testing procedure (see methods section). Supplementary figure 3.6 shows the null distributions of NMI values per module, resulting from the permutation procedure, along with the actual similarity (indicated by a dot) between the two age groups.



Supplementary figure 3.6: The null distribution of NMI values resulting from the permutation testing procedure is shown in the boxplots. The black dot represents the actual NMI value of the correspondence between the two age groups. Significant differences in module decomposition were only observed in the visual module and the DMN&FPCN module.

# Chapter 4

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## Flexibility of functional connectivity in the aging brain

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Flexible connectivity in the aging brain revealed by task modulations. *Human Brain Mapping*. 2013.

## 4 Flexibility of functional connectivity in the aging brain

### 4.1 Abstract

Recent studies have shown that aging has a large impact on connectivity within and between functional networks. An open question is whether elderly still have the flexibility to adapt functional network connectivity (FNC) to the demands of the task at hand. To study this, we collected fMRI data in younger and older participants during resting state, a selective attention task and an n-back working memory task with varying levels of difficulty. Spatial independent component (IC) analysis was used to identify functional networks over all participants and all conditions. Dual regression was used to obtain participant and task specific time courses per IC. Subsequently, functional connectivity was computed between all ICs in each of the tasks. Based on these functional connectivity matrices, a scaled version of the eigenvector centrality (SEC) was used to measure the total influence of each IC in the complete graph of ICs. The results demonstrated that elderly remain able to adapt FNC to task demands. However, there was an age-related shift in the impetus for FNC change. Older participants showed the maximal change in SEC patterns between resting state and the selective attention task. Young participants, showed the largest shift in SEC patterns between the less demanding selective attention task and the more demanding 2-back task. Our results suggest that increased FNC changes from resting state to low demanding tasks in elderly reflect recruitment of additional resources, compared to young adults. The lack of change between the low and high demanding tasks suggests that elderly reach a resource ceiling.

### 4.2 Introduction

Functional connectivity is an important measure that can be used to assess information transfer between brain areas. Numerous studies have demonstrated the existence of different functional networks. These are defined as groups of brain areas that tend to show high functional connectivity and have a particular functional signature (Biswal et al., 1995; Greicius et al., 2003; Sporns et al., 2004). There is ample evidence for a relation between functional connectivity patterns and specific task demands in young participants. For example, Hampson et al. (2002) showed that functional connectivity between language-related brain areas increased when participants listened to speech compared to resting state. In addition, Shirer et al. (2011) found that connectivity increased between the dorsal attention network (DAN) and the basal ganglia during a subtraction task compared to resting state. These, and similar findings (e.g. Dew et al., 2012; Hare et al., 2010; Sala-Llonch et al., 2012; Sterpenich et al., 2006; Wolbers et al., 2006), illustrate that connectivity within and between (functional) networks is dependent on task demands.

There is strong evidence that connectivity within specific functional networks, that are involved in higher level cognitive functioning, is reduced in elderly (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Grady et al., 2010; Sambataro et al., 2010). However, connectivity between different functional networks tends to increase in older compared to younger adults (Geerligs et al., 2012a). These functional connectivity changes affect cognitive functioning in elderly. For example, a decrease in connectivity within the default mode network (DMN) has been linked to deterioration in performance on processing speed and working memory tasks in elderly (Andrews-Hanna et al., 2007; Sambataro et al., 2010).

Most aging studies so far, have focused on age-related changes in brain activity. These studies have provided evidence that the adaptation of brain activity to task demands proceeds differently in younger and older adults. Older adults often show additional activation compared to young adults, specifically in prefrontal areas, when comparing a task performance to a baseline condition, as well as comparing increasing levels of task demands (Cabeza, 2002; e.g. Cabeza et al., 2004; Madden et al., 1999; Mattay et al., 2006; Reuter-Lorenz et al., 2000). It has been suggested that these increased activations reflect the response of the brain to processing inefficiencies, leading to the recruitment of additional or “reserve” resources (Reuter-Lorenz and Cappell, 2008; Stern et al., 2005). The downside of this additional recruitment is that older adults appear to reach a resource ceiling as the task demands increase further. At this point, activation does not increase anymore and might even decrease, which is associated with a drop in task performance (Reuter-Lorenz and Cappell, 2008).

Although many studies have demonstrated the differences between younger and older groups in adaptation of brain activation to task demand, it is not known whether elderly are able to adapt the connectivity between different brain networks to the demands of the task at hand, in a similar manner as young adults. This question is especially important in the context of the age-related changes in connectivity both within and between functional networks that have been observed. Previous work by Spreng and Schacter (2011) has provided a first indication that flexibility of interactions between networks is reduced in older adults. They demonstrated that in younger adults the fronto-parietal control network (FPCN) was flexibly coupled to either the DMN or the DAN, depending on the task demands (involving autobiographical memory or visuo-spatial planning, respectively). In older adults, this flexibility was reduced and the FPCN was coupled with the DMN in both task conditions.

In the current study we focus on connectivity between functional networks, that is, functional network connectivity (FNC). A procedure to study FNC was first described by Jafri and colleagues (2008). This procedure is based on the identification of different functional networks, using spatial independent component analysis (ICA). ICA can be applied to decompose fMRI data into a set of maximally spatially independent voxelwise



maps and their corresponding time-courses (Calhoun et al., 2001). Although the resulting spatial maps of independent components are maximally independent, their corresponding time-courses can show considerable temporal correlations. Therefore, the temporal correlations between different ICs or “functional networks” can be computed and compared between different conditions (Arbabshirani et al., 2012). It should be noted that there is no fixed number of functional networks in the brain. The number of networks that is identified in a given study depends on the scale on which these networks are investigated. If one were to investigate on a smaller scale, functional networks can generally be split again into distinct sub networks (Meunier et al., 2009b; Meunier et al., 2010).

This method allows testing whether functional connectivity between pairs of ICs is modulated by particular task demands. However, a disadvantage of this approach is that it requires a large number of multiple comparisons. Alternatively, task related modulations of functional connectivity can be indexed by looking at centrality (Lohmann et al., 2010); a class of graph theoretical measures that can be used to assess the prominence or functional importance of each IC, within the complete graph of ICs. A graph is a schematic representation of a network, which consists of a set of nodes (in this case the ICs) and edges (the connections between them). Depending on the number and positioning of the edges, one IC can be more central in the graph than another. Task related changes in centrality can be used as an index of adaptations to task demands. The centrality of an IC can be measured in a number of different ways. The simplest way to define centrality of an IC is to look at its degree, defined as the number of connections an IC has with other ICs. Degree defines an IC with many connections as more central in the graph than an IC with few connections (Freeman, 1979). However, the degree is not able to measure the influence of an IC throughout the graph. Therefore, we instead used the eigenvector centrality, to capture not only the direct connections of an IC but also its influence throughout the graph (Bonacich, 1972; Bonacich, 2007). Eigenvector centrality can be seen as a sum of all direct connections, weighted by the centrality of indirect connections, thereby taking into account the entire connectivity pattern.

In the current study, fMRI was recorded in both younger and older participants during eyes closed resting state, during a selective attention task and during a working memory task. Functional networks are each involved in certain (cognitive) functions. It is likely that depending on the demands of the task at hand, different ICs will play a more central role in the graph of ICs. Therefore, it is expected that the pattern of eigenvector centrality over ICs will change depending on the task at hand. To this end, we used correlations to investigate the similarity of eigenvector centrality over all ICs between different experimental conditions. For example, if the FNC is independent of a specific task, we would expect the eigenvector centrality pattern in the tasks to be similar, that is, we would expect a high correlation over ICs. On the other hand, low correlations would reflect a task or condition dependent change in eigenvector centrality. The main aim of our study was to assess

whether condition-related changes in eigenvector centrality patterns were dependent on age; are elderly able to flexibly adapt FNC to the demands of the task at hand, similar to young adults? Based on effects of aging on brain activity as discussed above, it could be hypothesized that older participants adapt FNC patterns to the task demands in a different way than young. By comparing the similarity of eigenvector centrality patterns between younger and older participants across conditions, we can assess differences in the age-related modulation of FNC. In addition, we examined these changes in more detail by investigating the age- and condition related changes in eigenvector centrality, separately for each IC.

## 4.3 Methods

### 4.3.1 Participants

Forty younger (21 males,  $M_{\text{age}} = 20.6$  years, range: 18-26 years) and 40 older adults (24 males,  $M_{\text{age}} = 64.9$  years, range: 59-74 years) participated in the experiment after giving informed consent. All participants were right handed and had no history of neurological or psychiatric disorders. They had normal or corrected-to-normal visual acuity. All participants scored 26 or higher on the Mini Mental State Examination (MMSE, Folstein et al., 1975) and below 16 on both subscales of the Hospital Anxiety and Depression Scale (HADS, Zigmond and Snaith, 1983). The study adhered to the Declaration of Helsinki and was approved by the local ethics committee of the University Medical Center Groningen, the Netherlands. Data of one young and one older participant were lost due to technical problems. One older participant was excluded because a brain abnormality was detected.

### 4.3.2 Procedure and cognitive tasks

fMRI data was recorded in three different runs, in which participants performed an n-back task, a selective attention (SA) task and 10-minutes of resting state. A schematic display of the selective attention as well as the n-back task is presented in Figure 4.1. During resting state, participants were instructed to keep their eyes closed, but not to fall asleep. Results on each of these conditions separately will be reported elsewhere. The order of the tasks was randomized over participants. For both tasks, stimulus generation and response collection were controlled using E-prime 1.2 (Psychology Software Tools, Inc., Sharpsburgh, PA). Participants viewed the stimuli via a mirror mounted on the head coil. In both tasks a fixation cross remained on screen throughout the task presentation. Responses were given by pressing a button with the right index or middle finger. The specific association between the button and the response finger was randomized over participants.

### 4.3.2.1 N-back task

The n-back task had three load conditions; 0-, 1- and 2-back. Each block started with the presentation of task instructions. Subsequently, in each trial participants were presented with a single stimulus letter (500 msec). Each letter was randomly positioned in one of 8 possible locations (horizontal X axis, vertical Y axis and the lower and upper position of both diagonals). The inter trial interval varied randomly between 1000 and 2000 msec. In the 0-back load condition, the target was the letter 'x'. In the 1-back load condition, the target was any letter identical to the letter immediately preceding it. In the 2-back load condition, the target was any letter identical to the letter presented 2 trials ago. The visual input was identical for all loads and the conditions could only be differentiated through the instructions received. Each load condition was presented twice, resulting in a total of 6 task blocks, with 100 trials each. In each block, targets occurred randomly in 50 % of the trials. Blocks were followed by a 30 second fixation cross. The order of the task loads was semi-randomized between participants. Letters were randomly presented either in upper-case (50%) or lower-case (50%). Participants were instructed to ignore the case of the letter and to focus on its identity. The letters were chosen from a set of 18 consonants derived from the Dutch alphabet (all consonants except the letters Q, Y and J).

### 4.3.2.2 Selective attention task

After general task instructions, 6 experimental blocks, each containing 63 trials were presented. At the start of a block, participants were presented with a target letter (5 sec), followed by a cue frame, indicating on which diagonal (right-up, left-up) relevant information would be presented. In each trial, the stimuli, consisting of 4 letters positioned at the end points of both diagonals, were presented for 300 msec followed by an interstimulus interval varying randomly between 2000 and 2500 msec. Participants were required to press the 'yes' button when the target letter was presented on a relevant diagonal position [target]. In all other cases (i.e., target letter on irrelevant diagonal positions [irrelevant target] or no target letter presented [nontarget]) they should press 'no'. Relevant target trials made up 33% of the total number of trials. There were never two target letters present in one stimulus frame. Stimulus letters were randomly chosen from the alphabet, excluding the letters g, i, o, q, u, x, and y. Each block was followed by a 30 second fixation cross.

### 4.3.3 Behavioral data

Participants were excluded based on behavioral data if there were indications that they did not understand/follow the task instructions. Data of three younger participants and one older participant were excluded because their accuracy on the SA task was around or

below chance level (below 60%) in one or more task conditions (targets, nontargets and/or irrelevant targets). For the n-back task, all participants performed the 0- and 1-back task with over 70% accuracy, indicating that the task instructions were clear. On the 2-back task, 4 participants performed around or below chance level (below 60% accuracy). However, this likely reflects the difficulty of the task and not the lack of understanding of task instructions. Therefore data of these participants were included in the analysis. Thus, the behavioral and ICA analyses were performed on the data of 36 younger and 37 older participants. For each participant and each task the median reaction time for correct responses and the mean accuracy scores were used in subsequent analyses. Fast guesses (responses faster than 200 msec) and responses slower than the minimum interstimulus interval (1500 msec for the n-back task and 2000 msec for the SA task) were regarded as incorrect responses.

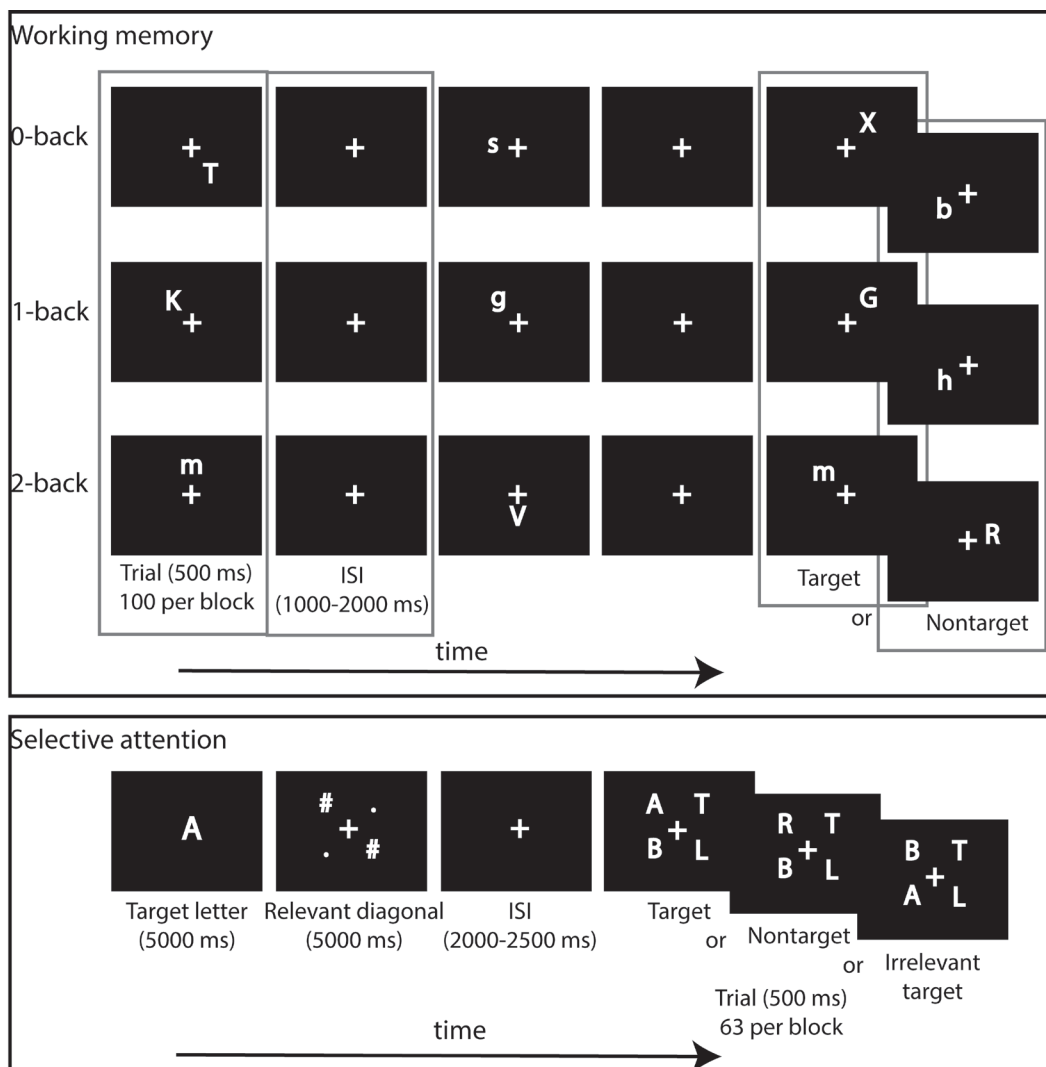


Figure 4.1: Schematic description of the n-back and the selective attention tasks.

### 4.3.4 Image acquisition

FMRI scans were obtained with a three tesla MR scanner (3T Achieva, Philips Medical Systems, Best, Netherlands), with echo planar imaging (EPI) capability and an eight channel SENSE head coil. Functional images were obtained with the following pulse sequence parameter settings: single shot EPI; 37 slices; slice thickness = 3.5 mm; no gap; field of view = 224 mm; matrix scan size 64 by 64; transverse slice orientation; repetition time (TR) = 2000 msec; echo time (TE) = 30 msec; minimal temporal slice timing = 1836 msec; flip angle 70°. A 3-D T1-weighted anatomical scan of the entire brain was obtained for each participant using the following pulse sequence parameters: field of view = 256 mm; matrix scan size 256 by 256; 170 slices; slice thickness 1 mm; transverse slice orientation; TE = 3.6 msec; TR = 9 msec; flip angle 8°.

### 4.3.5 fMRI data analysis

Offline processing was performed using the statistical parametric mapping software package (SPM 8; <http://www.fil.ion.ucl.ac.uk/spm/software>). The functional images were motion-corrected and coregistered to the anatomical scan. The coregistration was checked visually and adjusted manually when required. Bias regularization (SPM 8) was used to reduce signal intensity variations due to field inhomogeneities in both structural and functional images. For functional images, the regularization was initially applied to the first and the last functional scan within each run. Based on these two corrections, an average correction factor was computed for each voxel, which was applied to all scans in each run. A group specific anatomic template was created (for young and elderly participants together), using Diffeomorphic Anatomical Registration Exponentiated Lie algebra (DARTEL), to optimize inter-participant alignment (Ashburner, 2007). Data were smoothed with an 8 mm full-width half maximum (FWHM) Gaussian kernel.

### 4.3.6 Independent component analysis

Data were decomposed into functional networks using a group-level spatial independent component analysis (ICA) as implemented in the GIFT toolbox (version 2.0e, <http://mialab.mrn.org/software/gift/>). The data from the two tasks and resting state were entered as separate runs in the analysis. Prior to ICA decomposition, voxel time series were z-scored to normalize variance across space (similar to Allen et al., 2012). This procedure is aimed at minimizing a possible bias in subsequent variance-based data reduction steps due to variance differences between tasks and participants. The number of components in each run of each participant was estimated by the minimum description length (MDL) criterion (Li et al., 2007). The mean estimated number of components was 38; therefore the data was decomposed into 38 functional networks. To monitor the reliability of the

ICA decomposition, we repeated the Infomax ICA algorithm (Bell and Sejnowski, 1995) 10 times in the ICASSO toolbox within GIFT (<http://www.cis.hut.fi/projects/ica/icasso>). With each repetition, the ICA algorithm was initialized with a different start point. Generally, these results showed compact clusters, validating the reliability of component estimation. After IC components had been established on the group level, part of the dual regression procedure was applied to estimate participant- and run specific time courses (Filippini et al., 2009). This was done by regressing the group spatial maps into the 4D dataset of each subject and each run. This procedure ensures that the IC timecourse for each participant and each run is based on the same spatial map. A subset of 25 ICs was visually selected for further analysis, based on the expectation that ICs should exhibit peak activations in grey matter and low spatial overlap with known vascular, ventricular, motion, or susceptibility artifacts.

### 4.3.7 Functional connectivity analysis

Prior to the functional connectivity analysis, we applied a number of additional processing steps to the time-courses of each participant and each run to remove variance in the data related to participant motion and scanner drifts (Van Dijk et al., 2010). A flow chart of the analysis procedure is presented in figure 4.2. The default procedure in GIFT is to detrend the linear, quadratic and cubic trends in the time-courses. Subsequently, residual effects of motion were corrected by regression with the 6 realignment parameters and their temporal derivatives. In addition, variance associated with stimulus presentation was removed in the SA-task and the n-back task, to make sure that connectivity is not dominated by synchronized stimulus-evoked responses (Al-Aidroos et al., 2012; Geerligs et al., 2012a). For the SA task, target, nontarget and irrelevant target trials were modeled as separate regressors. In addition regressors related to task instructions and error trials were modeled in separate regressors. For the n-back task, 0-back, 1-back and 2-back trials were modeled as separate regressors in addition to regressors for the task instructions. In both tasks, we convolved all regressors with the canonical hemodynamic response function (HRF), as well as the temporal derivative and the dispersion derivative to account for local variability in the shape of the HRF. The residuals of this procedure were used to compute functional connectivity. The resulting functional connectivity reflects background connectivity, which can be used to assess how the cognitive state of a participant affects the functional architecture of the brain (Al-Aidroos et al., 2012).

An additional movement correction procedure was performed to make sure that the effects of age and task condition on functional connectivity were not due to spurious effects of motion. To this end, we used part of the procedure applied by Power and colleagues (2012). The first step in this correction procedure was to calculate the total displacement per scan. The rotational parameters were transformed to millimeters (mm) displacement by assuming affected voxels were at a distance of 65 mm from the origin

of the rotation. The total displacement per scan was computed using the procedure in the ArtRepair toolbox <http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html>. Scans in which the displacement compared to the previous scan was larger than 0.5 mm were flagged. The flagged scans as well as two scans before and one scan after this scan were not taken into account in the computation of the correlation matrix.

In addition to movement differences, a bias might be introduced due to the differing numbers of scans in each task condition; 300 resting state scans, +/- 200 scans per n-back load condition and +/- 480 scans for the SA task. Therefore, we randomly selected up to 200 scans (depending on the number of scans left after movement correction) out of all scans for both the resting state and the SA condition, to make the number of scans equivalent to each n-back load condition. These scans were then used to compute the correlation matrix. Those participants (4 younger and 2 older) for which fewer than 150 scans remained in one or more conditions due the movement correction procedure were excluded from the functional network connectivity analysis. Thus, the functional network connectivity analysis was performed on the data of 32 younger and 35 older participants

Condition specific time series were generated by segmenting time-courses from each IC into separate condition blocks. Each block started 3 scans after the first stimulus onset and ended at the final stimulus onset of that block. For the n-back task, there were two 0-back blocks, two 1-back blocks and two 2-back blocks. For the SA task, there were 6 experimental blocks. The time course of each block segment was mean centered and concatenated with segments of the same condition. Subsequently the correlation coefficient was computed between the time courses for each pair of ICs for each participant and each condition. The Spearman rank correlation was used to reduce the effect of outliers on the correlation estimate.

### 4.3.8 Eigenvector centrality

To determine the functional importance of each IC, we used a graph theoretical approach. The ICs are taken as the separate nodes in a graph, whereas the functional connections between ICs represent the graph's edges. Eigenvector centrality was computed for each node, for each condition and each participant separately (Lohmann et al., 2010). A node is considered to be central if it has many connections as well as high connectivity strengths to other nodes, particularly when these other nodes have a large number of connections -preferably with a high connectivity themselves (Bonacich, 1972). Eigenvector centrality can be seen as a weighted sum of the direct and the indirect connections of a node (Bonacich, 2007), that is, it takes the entire pattern of connections within a graph into account. Moreover eigenvector centrality does not depend on a pre-specified threshold for correlation values, unlike other centrality measures such as degree



or betweenness centrality.

Eigenvector centrality is based on an eigenvector decomposition of the adjacency matrix ( $A$ ). If we define  $\lambda_{max}$  as the largest eigenvalue and  $x_{max}$  as the corresponding eigenvector then  $Ax_{max} = \lambda_{max} x_{max}$ . The eigenvector centrality of a node  $i$  is then defined as  $x_{max,i}$ . The eigenvector centrality represents the relative influence of a node on all other nodes. Therefore, a graph with a higher average correlation coefficient will not always result in higher centrality values. Because we were interested in the total influence of a node on all other nodes, we applied an additional scaling by the largest eigenvalue  $\lambda_{max}$ . Here we employed that the largest eigenvalue  $\lambda_{max}$  of a positive correlation matrix is closely related to the mean of this positive correlation matrix (Friedman and Weisberg, 1981). Scaling the relative contribution per node (eigenvector centrality) with the total influence all nodes have on each other ( $\lambda_{max}$ ), thus results in a measure of the total influence per node, the scaled eigenvector centrality (SEC):  $SEC_i = x_{max,i} \lambda_{max}$ .

To calculate the eigenvector centrality, it is required that the eigenvector decomposition has a unique solution. To achieve this, all values in the adjacency matrix must be positive. Lohmann et al (2010), proposed two methods to meet this requirement: either to add a constant to the correlation values, using  $\tilde{r} = r + 1$  or to use the absolute values of the correlation coefficient  $\tilde{r} = |r|$ , where  $r$  is the correlation and  $\tilde{r}$  is the adapted version. Using the first alternative will result in a low eigenvector centrality for nodes with high negative correlations, underestimating the strength of the influence of these nodes. The second alternative, on the other hand, takes only the strength of the correlation into account and not the sign. However, since a node with a strong negative correlation can be regarded as a node with a high influence on other nodes in the graph, we chose this second approach.

#### 4.3.9 Statistical analysis

The main aim of this study was to investigate whether elderly are able to flexibly change patterns of functional connectivity between networks (FNC) depending on task demands. General changes in FNC patterns were measured by correlating the SEC over all ICs in one condition with the SEC over all ICs in another condition. This results in one Spearman rank correlation coefficient per participant, per comparison between conditions. These correlation values were transformed to a normal distribution using Fisher  $r$  to  $z'$  transformation (Fisher, 1921). For each combination of conditions, the transformed scores were then compared between age groups using an independent samples t-test in SPSS. To reduce the number of comparisons, analyses were initially restricted to the resting state, SA and 2-back conditions, as these are most distinct in terms of the cognitive processes they require. The 0-back and 1-back task conditions were used for post-hoc testing to confirm specific patterns observed in the data.

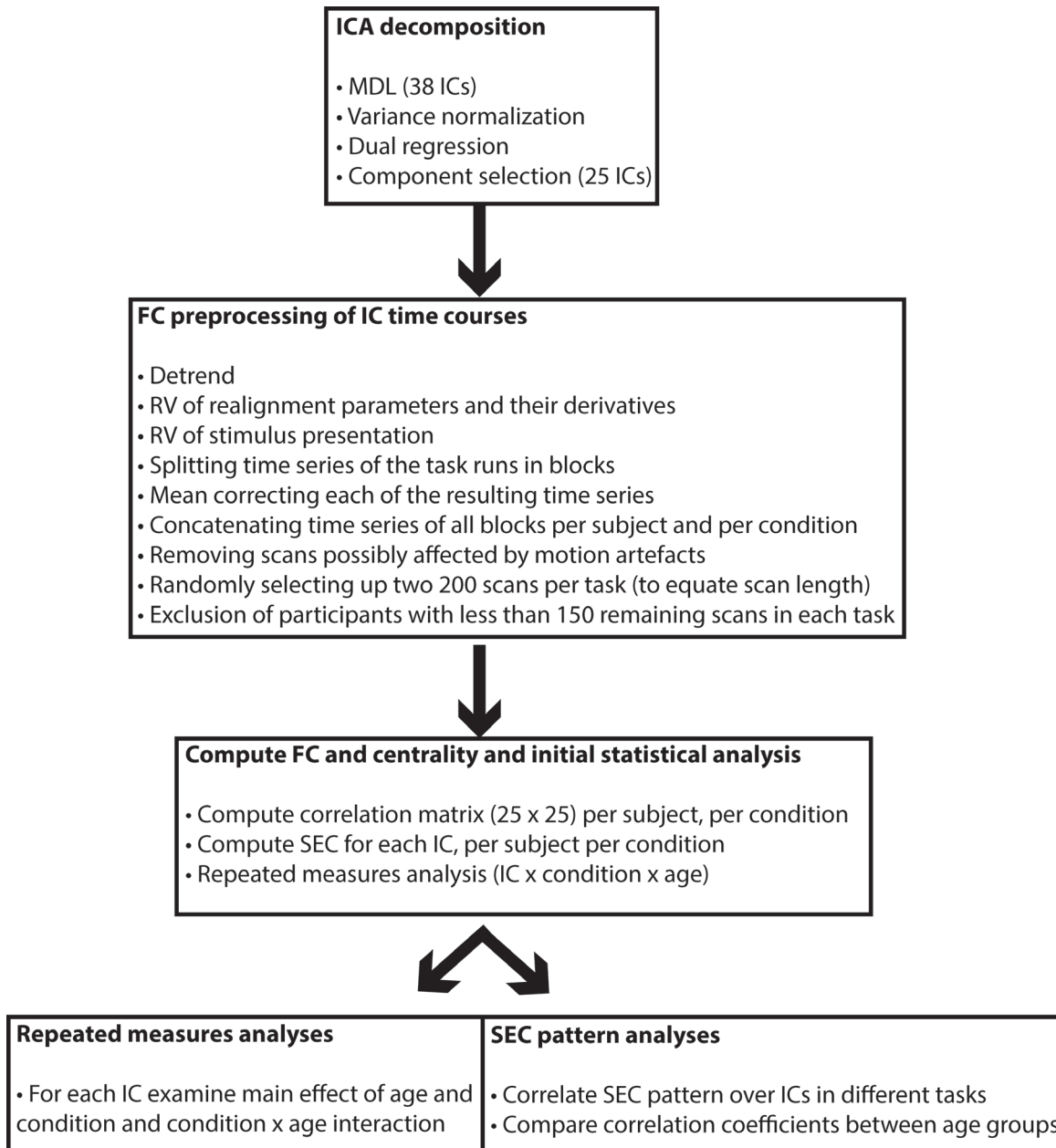


Figure 4.2: Flow chart of all steps in the analysis procedure after the initial, standard preprocessing steps. RV=removal of variance, SEC=scaled eigenvector centrality, FC=functional connectivity, ICA=independent component analysis, MDL=minimal description length.

To examine the effects of age groups and task on SEC, repeated measures analysis were used. Initially, we used a model with the within subject factors task (rest, SA-task and 2-back task) and IC and the between subject factor age group. Subsequently, repeated measures analyses were created per IC, with the within subject factor task and the between subject factor age group. As this resulted in 25 different models, the reported p-values of this analysis were corrected for multiple comparisons, using the FDR correction (Benjamini and Hochberg, 1995). P-values were adjusted for violations of the sphericity assumption using the Greenhouse-Geisser correction (Greenhouse and Geisser, 1959). Only results with an FDR corrected p-value equal to or below 0.01 are reported. This stringent threshold was chosen to limit the number of false positives

resulting from the 75 tests performed. For clarity, uncorrected degrees of freedom values are presented in the results section. Paired and independent samples t-tests were used for post-hoc testing. Prior to the analyses, SEC values were transformed as described by van Albada and Robinson (2007) to ensure that they obey a Gaussian normal distribution, maintaining the mean and standard deviation of the original distribution.

To explore whether the SEC is related to task performance we created regression models for each of the ICs for which an interaction effect between task and age group was observed. For each of the task conditions (SA and 2-back), the accuracy and reaction times during task performance were used as the dependent variables in separate models. Age group and the SEC of the respective IC were used as the independent variables, along with the interaction between the two. This resulted in a total of sixteen regression models. No correction for multiple comparisons was applied to these post-hoc tests.

## 4.4 Results

### 4.4.1 Behavioral data

In all tasks, older participants responded slower than younger participants ( $F(1,71)=116.6$ ,  $p<0.001$ ), however the differences between age groups varied with condition ( $F(3,213)=19.83$ ,  $p<0.001$ , see table 4.1). Differences between age groups were largest in the 2-back task condition (237 msec), smaller in the 1-back task condition (161 msec) and the SA task (154 msec) and smallest in the 0-back task condition (116 msec). In both age groups, participants were faster in the 0-back than the 1-back task condition ( $t(72)=14.04$ ,  $p<0.001$ ) and faster in the 1-back than the 2-back task condition ( $t(72)=14.48$ ,  $p<0.001$ ). In the SA task, participants were faster than in the 0-back task condition ( $t(72)=7.59$ ,  $p<0.001$ ) but slower than in the 1-back task condition ( $t(72)=5.22$ ,  $p<0.001$ ).

Table 4.1: Averages and standard deviations for response times (RT) and accuracy (ACC), separately for each age group and task (condition)

	0-back	1-back	2-back	SA
RT young (msec)	483 (50)	534 (60)	650 (104)	506 (68)
RT old (msec)	600 (54)	695 (81)	888 (108)	660 (80)
ACC young (%)	94 (3)	90 (5)	86(4)	95(3)
ACC old (%)	94(3)	90(4)	73 (12)	95 (4)

In the 2-back task condition, older participants had significantly lower accuracy scores than young participants ( $t(71)=6.08$ ,  $p<0.001$ ), whereas there were no significant differences between the age groups in the other tasks and conditions (age x condition;

$F(3,242)=30.77, p<0.001$ ). In both age groups, accuracy scores were higher in the 0-back than the 1-back task condition ( $t(72)=7.63, p<0.001$ ) and higher in the 1-back than in the 2-back task condition ( $t(72)=8.07, p<0.001$ ). Accuracy scores in the SA task were slightly higher than in the 0-back task condition ( $t(72)=2, p=0.049$ ).

#### 4.4.2 Independent components

From the 38 estimated IC components, 25 components were selected as nonartifactual, relevant networks. These components were derived from all the rest and task data together. Figure 4.3 illustrates the spatial maps of these components. For clarity and ease of display, these ICs were grouped based on function, using a similar approach as Allen et al. (2012). A description of the ICs can be found in the caption of figure 4.3.

For each IC, we used the scaled eigenvector centrality (SEC) to investigate its centrality or importance in the graph. SEC reflects the total influence of an IC in the graph of ICs, by capturing both the correlation strength and the number of connections of that IC to other ICs, as well as the centrality of the neighboring (i.e. connected) ICs. To investigate whether SEC changes in different ICs depend on age-group and condition, a repeated measures analysis was performed. We observed a main effect of IC ( $F(24,3120) = 28.6, p<0.001$ ), a main effect of task ( $F(2, 3120)=11.49, p<0.001$ ) and a main effect of age group ( $F(1,65) = 12.36, p=0.001$ ), as well as, significant interactions between task and IC ( $F(48,3120) = 9.08, p<0.001$ ), age and IC ( $F(24,3120) = 6.09, p<0.001$ ), and age, task and IC ( $F(48,3120) = 4.16, p<0.001$ ). To elucidate these effects we created a repeated measures model for each IC, with the within subjects factor task and the between subjects factor age group. This allowed us to investigate differences in SEC between the two age groups, differences between the conditions as well as interactions between age and condition, separately for each IC. Averages and standard deviations for the SEC can be found in supplementary table 4.1, separately for each IC, condition and age group.

#### 4.4.3 Effects of age on SEC

Older participants had higher SEC values than younger participants in 4 of the 25 identified ICs, indicating that connectivity between functional networks was increased in older compared to younger participants. In particular in two of the four visual ICs, the basal ganglia and the anterior cingulate IC, older participants had higher SEC values than younger participants. Note that this description of results only takes into account the ICs in which there was no interaction between age and condition. Younger participants had a higher SEC than older participants in the medial frontal IC. In table 4.2, all main effects of task and age are described.

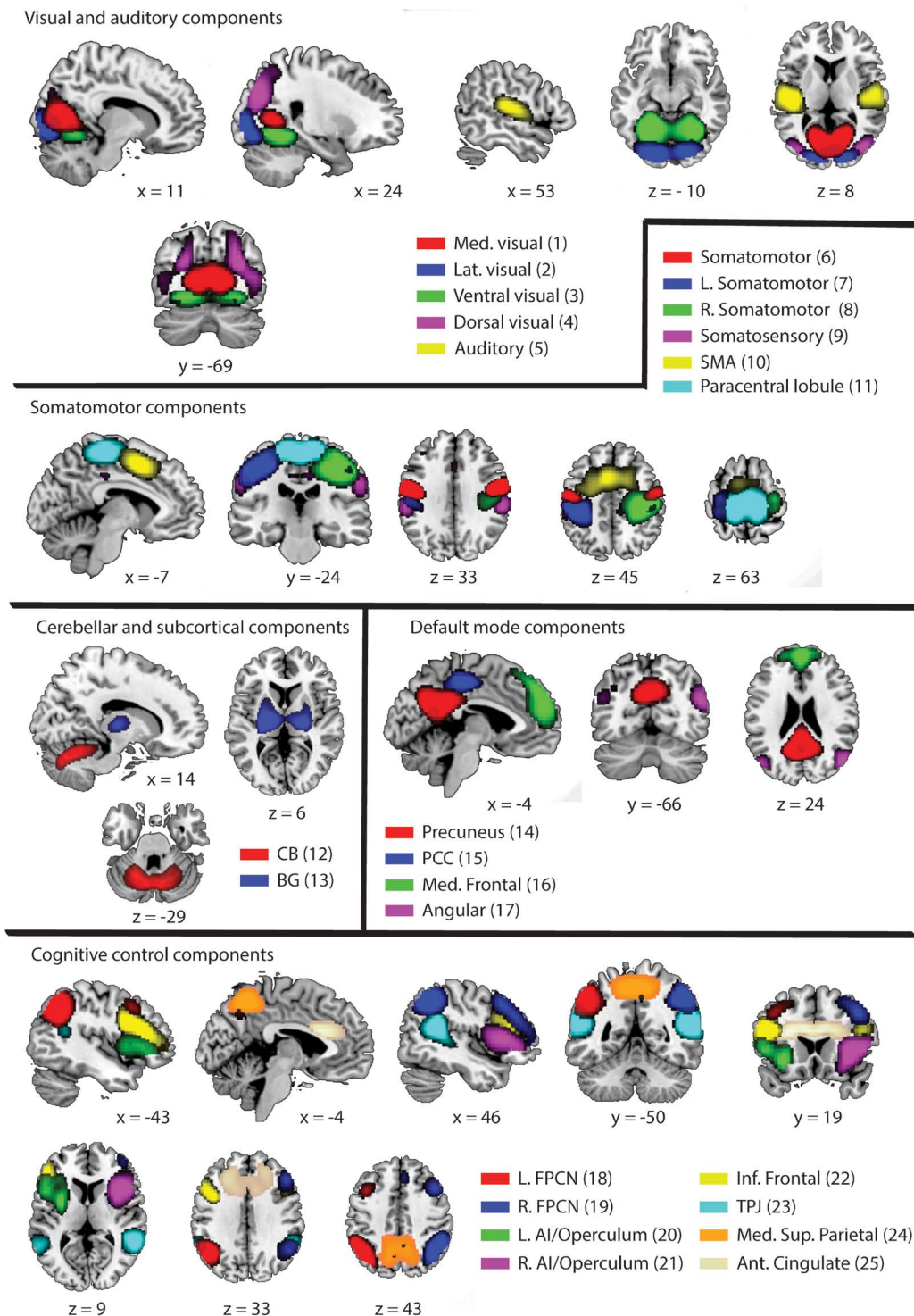


Figure 4.3: Identified independent components (ICs), grouped by location and function. The number between brackets indicates the independent component number. Within the identified ICs, there were 4 visual components, representing the medial (IC1), lateral (IC 2), ventral (IC3) and dorsal (IC4) parts of the visual system. In addition, one auditory component (IC 5) was identified. Six different components were identified that are related to sensorimotor functions (IC 6-11). Separate ICs were identified for the cerebellum (IC 12) and the basal ganglia (IC 13). The classical default mode network was represented in 4 separate components (IC 14-17). Separate left and right fronto-parietal components were identified (IC 18 and 19, respectively) as well as left and right anterior insula/opercular networks (IC 20 and 21, respectively).



Bilateral inferior frontal (IC 22) and temporo-parietal junction components (IC 23) were identified as well as medial superior parietal (IC 24) and anterior cingulate components (IC 25). R=right, L=left, Ant=anterior, Inf=inferior, Sup=superior, Lat=lateral, Med=medial, SMA=supplementary motor area, CB=cerebellum, BG=basal ganglia, PCC=Posterior Cingulate Cortex, FPCN=fronto-parietal control network, AI=anterior insula, TPJ=temporoparietal junction

### 4.4.4 Effects of task on SEC

In the majority of ICs, the SEC was smaller in task conditions compared to resting state, indicating that between network connectivity was stronger during resting state than during task performance. In particular in the ICs related to visual or auditory information processing, as well as ICs related to sensorimotor functions and the basal ganglia IC, the SEC was larger in resting state than during task performance. Specifically in the inferior frontal IC we found that centrality was increased in the 2-back task compared to resting state. The selective attention task showed an increase in SEC compared to resting state in the angular gyrus IC and the inferior frontal IC. In other ICs, the effect of task was specific to one of the age groups; these results are discussed in the next section.

### 4.4.5 Interactions between task and age per IC

The averages in different tasks and age groups are visualized in figure 4.4 for those ICs that showed a significant interaction between task and age group. An interaction between task and age was observed in the somatosensory IC (IC 9). In younger participants, SEC was not significantly different between conditions, whereas in old participants the SEC increased from rest to the SA task ( $t(34)=2.63$ ,  $p=0.013$ ) and from the SA task to the 2-back task condition ( $t(34)=2.93$ ,  $p=0.006$ ). Therefore, in rest elderly had a lower SEC than young adults ( $t(65)=2.11$ ,  $p=0.039$ ), whereas in the 2-back task condition elderly had a higher SEC than young participants ( $t(65) =2.62$ ,  $p=0.011$ ).

For older adults, the SEC in the precuneus IC (IC 14) was larger in the 2-back task condition than in the SA task ( $t(34)=3.88$ ,  $p<0.001$ ) and in rest ( $t(34)=3.17$ ,  $p=0.003$ ), while in young adults SEC was higher in the SA task than the 2-back task ( $t(31)=2.23$ ,  $p=0.033$ ) while both tasks were not significantly different from rest. In the 2-back task condition the SEC in the precuneus was significantly larger in older than young adults ( $t(65) =4.31$ ,  $p<0.001$ ).

Another interaction between task and age group was observed in the right FPCN IC (19). The SEC was significantly larger in young than older participants during the 2-back task condition ( $t(65)=3.84$ ,  $p<0.001$ ), but not in rest or during the SA task. In young adults, SEC was largest in the 2-back task condition compared to the SA task ( $t(31)=5.47$ ,  $p<0.001$ ) and rest ( $t(31)=3.84$ ,  $p=0.001$ ). In the older adults, no significant differences were observed between the tasks.

## Flexibility of functional connectivity in the aging brain

Table 4.2: Results of repeated measures analysis; effects of condition, age group and the interaction of age group and condition on SEC.

IC	Main effect task		Post-hoc			Main effect age		Post-hoc	Interaction task x age	
	F	p	RE>SA	R>2B	SA>2B	F	p	O>Y	F	p
Med. Visual (1)	7.23	0.004	RE>SA		2B>SA	19.6	<0.001	O>Y		
Lat. Visual (2)	5.98	0.007	RE>SA							
Ventral visual (3)	12.95	<0.001	RE>SA	RE>2B						
Dorsal visual (4)						10.27	0.009	O>Y		
Auditory (5)	19.28	<0.001	RE>SA	RE>2B	2B>SA					
Somatomotor (6)	24.66	<0.001	RE>SA	RE>2B	2B>SA					
L. Somatomotor (7)	13.70	<0.001	RE>SA	RE>2B	SA>2B					
R. Somatomotor (8)	19.31	<0.001	RE>SA	RE>2B						
Somatosensory (9)									8.36	0.004
SMA (10)										
Paracentral lobule (11)	10.81	<0.001	RE>SA		2B>SA					
CB (12)										
BG (13)	5.39	0.011	RE>SA			50.35	<0.001	O>Y		
Precuneus (14)									10.32	0.004
PCC (15)										
Med. Frontal (16)	5.49	0.010			SA>2B	16.49	<0.001	Y>O		
Angular (17)	12.39	<0.001	SA>RE		SA>2B					
L. FPCN (18)										
R. FPCN (19)									7.74	0.007
L. AI/Operculum (20)										
R. AI/Operculum (21)	7.23	0.002	RE>SA	RE>2B						
Inf. Frontal (22)	24.67	<0.001	SA>RE	2B>RE	2B>SA					
TPJ (23)									12.95	<0.001
Med. Sup. Parietal (24)										
Ant. Cingulate (25)	6.23	0.005	RE>SA	RE>2B		48.30	<0.001	O>Y		

Y=young, O=old, RE=rest, SA=selective attention task, 2B=2-back task, R=right, L=left, F=F-value, p=p-value, Ant=anterior, Inf=inferior, Sup=superior, Lat=lateral, Med=medial, SMA=supplementary motor area, CB=cerebellum, BG=basal ganglia, PCC=Posterior Cingulate Cortex, FPCN=fronto-parietal control network, AI=anterior insula, TPJ=temporoparietal junction, degrees of freedom for the F-test of the task and the interaction effect were 2 and 130, degrees of freedom for the F-test of the age effect were 1 and 65. Main effects of age and task are not displayed for those ICs that demonstrated a significant interaction of task\*age.



In the temporoparietal junction (TPJ) IC (23), similar SEC values were observed in both age groups in rest, while the SEC was larger in older than young adults in both the 2-back task condition ( $t(65)=3.31, p=0.002$ ) and the SA task ( $t(65)=5.35, p<0.001$ ). In young participants, SEC was smaller in the SA task compared to the 2-back task condition ( $t(31)=5.5, p<0.001$ ) and rest ( $t(31)=2.5, p=0.018$ ). In contrast, SEC in the older participants was larger in the 2-back task condition compared to the SA task ( $t(34)=2.52, p=0.017$ ) and larger in the SA task compared to rest ( $t(34)=4.63, p<0.001$ ).

We have performed additional analyses in which we have tested the effects of removing the variance associated with stimulus presentation prior to the computation of the connectivity matrix. The results of this procedure are described in the supplementary materials. They show that the main findings described above are robust and are only minimally affected by the specific approach used. In addition, to demonstrate the effect of the specific threshold selected for the analysis, results of the analyses are also presented for a lower significance threshold ( $p_{\text{fdr}} < 0.05$ ) in supplementary table 4.2.

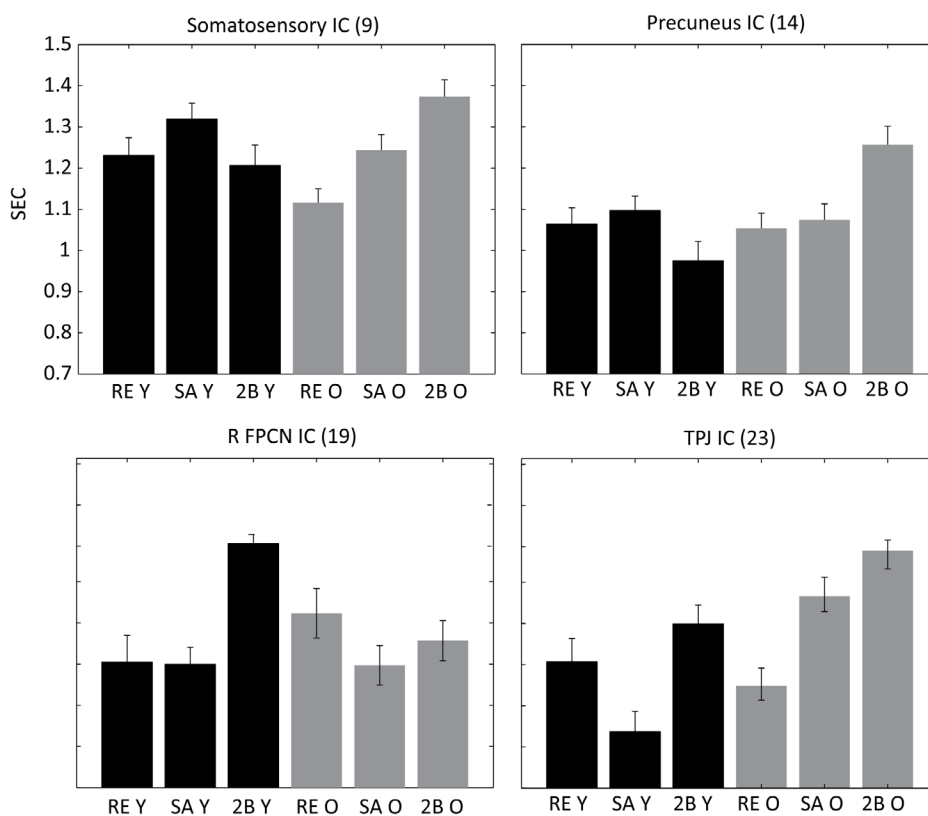


Figure 4.4: SEC for the different conditions and age groups, displayed for those ICs showing a significant interaction between age and task. Black bars show the mean and standard error of the SEC in younger participants, gray bars show the SEC in older participants. RE=rest, SA=selective attention task, 2B=2-back task, Y=young, O=old, FPCN=fronto-parietal control network, TPJ=temporoparietal junction.

#### 4.4.6 Effects of age on changes in SEC patterns with changing task demand

In the second approach to shed more light on the IC x age x task interaction, we focused on the relation between different ICs. Specifically, we examined the change in the SEC patterns across ICs between different task conditions and the effects of aging on this change. Correlation analyses were used to investigate the similarity of SEC patterns over all ICs between different conditions. Little change between two conditions would be reflected in high correlation values (high similarity), whereas a large change between two conditions would result in low correlations (low similarity). Correlations were compared between age groups to see how changes between conditions are affected by aging.

#### 4.4.7 Differences in SEC patterns between resting state and task performance

The relative importance of nodes, i.e. the SEC pattern, was similar in resting state and the SA task in young participants (z-transformed correlation:  $M=0.46$ ,  $SD=0.26$ ), whereas this similarity was reduced in older participants ( $M=0.17$ ,  $SD=0.28$ ;  $t(65)=4.35$ ,  $p<0.001$ ). For both younger and older adults there was little similarity between the SEC patterns in the 2-back task condition and rest (young:  $M=0.19$ ,  $SD=0.28$ ; old:  $M=0.12$ ,  $SD=0.22$ ;  $t(65)=1.03$ ,  $p=0.31$ ). The relatively high accuracy levels and the fast responses in the SA task suggest that the levels of cognitive demand required by this task are lower than the cognitive demand required in the 2-back task condition. Therefore, the results suggest that the change in SEC pattern is larger in older than younger participants only from resting state to low demanding tasks. To confirm this, we additionally considered the 0- and the 1-back task conditions. The accuracy levels and response times indicate that task demand in the 0-back task condition is similar to that in the SA task, while demand in the 1-back task condition is higher than in the 0-back task condition, but lower than in the 2-back task condition. Based on the effect of aging in the SA-task compared to resting state, we would expect the largest age group differences in the change in SEC pattern for the 0-back task condition versus resting state and a smaller age difference for the 1-back task condition versus resting state. Indeed, we found that the SEC pattern in the 0-back task condition was more similar to the resting state condition, in young ( $M=0.44$ ,  $SD=0.26$ ) compared to older adults ( $M=0.15$ ,  $SD=0.29$ ;  $t(65)=4.17$ ,  $p<0.001$ ). Likewise, the SEC pattern in the 1-back task condition was more similar to the resting state, in young ( $M=0.30$ ,  $SD=0.26$ ) compared to older adults ( $M=0.17$ ,  $SD=0.21$ ;  $t(65)=2.16$ ,  $p=0.035$ ). In figure 4.5 the age group differences in absolute changes in SEC between tasks and resting state are visualized per IC.

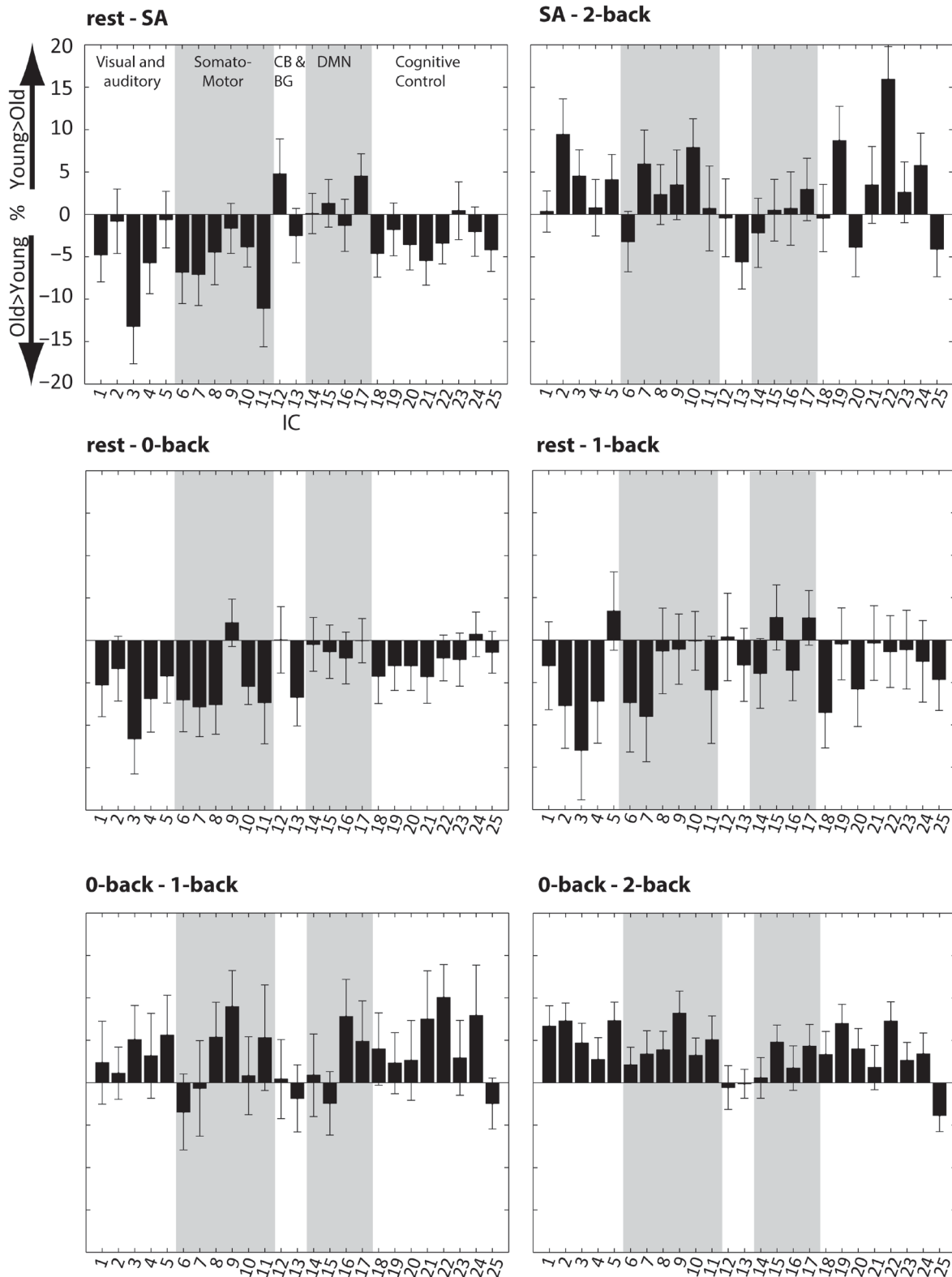


Figure 4.5: Visualization of the differences between age-groups in absolute change in SEC between task/rest conditions per IC. The bars represent differences between older and younger adults in absolute SEC change per IC. Differences are expressed as a percentage of the total difference between older and younger adults. The standard error of the mean is indicated by the error bars.

#### 4.4.8 Differences in SEC patterns between the selective attention task and n-back task conditions

In addition to the decreased similarity in SEC pattern between resting state and low demanding task conditions in elderly compared to young individuals, we observed an increased similarity in SEC pattern between different tasks in the elderly. The SEC patterns in the 2-back task condition and SA task were similar in older ( $M=0.44$ ,  $SD=0.29$ ) and less similar in younger adults ( $M=0.27$ ,  $SD=0.21$ ;  $t(65) = 2.7$ ,  $p=0.009$ ). In line with this result, elderly showed a more similar SEC pattern between the 0-back and the 2-back task condition (young  $M=0.25$ ,  $SD=0.30$ ; old  $M=0.58$ ,  $SD=0.33$ ;  $t(65) = 4.16$ ,  $p<0.001$ ) and showed a trend toward the same effect in the 0-back and the 1-back task condition (young  $M=0.51$ ,  $SD=0.33$ ; old  $M=0.67$ ,  $SD=0.34$ ;  $t(65) = 1.96$ ,  $p=0.054$ ). However, the age groups did not show a difference in SEC pattern similarity between (a) the 1-back and the 2-back task condition, (b) the 0-back task condition and the SA task, and (c) the 1-back task condition and the SA task (a: young  $M=0.53$ ,  $SD=0.26$ ; old  $M=0.60$ ,  $SD=0.31$ ;  $t(65) = 1.0$ ,  $p=0.32$ ; b: young  $M=0.57$ ,  $SD=0.32$ ; old  $M=0.50$ ,  $SD=0.33$ ;  $t(65)=0.83$ ,  $p=0.41$ ; c: young  $M=0.49$ ,  $SD=0.32$ ; old  $M=0.48$ ,  $SD=0.34$ ;  $t(65)=0.09$ ,  $p=0.93$ ). The differences between age-groups in SEC changes between task conditions are visualized in figure 4.5.

#### 4.4.9 Relation with behavior

Of the four ICs that showed an interaction between condition and age group, only the precuneus IC (14) showed a significant correlation with behavior. In the SA task, increased SEC of the precuneus IC (14) was related to increased accuracy ( $B=0.01$ ,  $t(63)=2.10$ ,  $p=0.04$ ), whereas no significant effect of age ( $B=0.007$ ,  $t(63)=0.70$ ,  $p=0.49$ ) and no interaction between age and SEC was observed ( $B=0.001$ ,  $t(63)=0.07$ ,  $p=0.95$ ). However, it should be noted that no correction for multiple comparisons was applied and that the F-test for the complete regression model was not significant ( $F(3,63)=1.63$ ,  $p=0.19$ ). Therefore, the observed relation could be a false positive result.

### 4.5 Discussion

To truly understand the effects of aging on brain function, it is important to know if elderly are able to adapt FNC in response to changing task demands. In this study, we investigated how aging affects the adaptation of functional connectivity between functional networks (FNC) to the demands of the task at hand. We have used a brain-wide approach to show that elderly can indeed adapt functional connectivity. However, the results show that the impetus to change FNC patterns changes with age; whereas young participants show the maximal change in connectivity patterns from less demanding to more demanding task conditions, older participants showed maximal change from rest

to low demanding tasks.

Previous studies have shown that during task performance, functional connectivity increases between specific areas that are involved in execution of the task at hand (e.g. Dew et al., 2012; Hampson et al., 2002; Hare et al., 2010; Sala-Llonch et al., 2012; Shirer et al., 2011; Sterpenich et al., 2006; Wolbers et al., 2006). Since, the SEC incorporates both direct and indirect functional connectivity from an IC to all other ICs, we would expect that, similar to functional connectivity, the SEC will increase in ICs that are functionally relevant to the task at hand. Indeed, the results of the current study demonstrate an increase in centrality of ICs that play an important role in task performance. During the 2-back task, we found that in both age groups, centrality was increased in the inferior frontal IC compared to resting state, an area that has been suggested to play an important role in working memory (Nagel et al., 2009; Owen et al., 2005). In addition, another network important for working memory, the right fronto-parietal control network, showed increased centrality in young participants during the 2-back task. Another study by Lohmann and colleagues (2010) has also shown that the eigenvector centrality increases in areas that are important in the condition at hand. More specifically, they found that the eigenvector centrality of the ventral striatum, a key region implicated in reward such as food, increased in a sated compared to a hungry condition. Note that the direction of correlations was not taken into account in the current analysis. Therefore it is unclear whether a SEC increase reflects an increase in negative correlations or an increase in positive correlations.

Especially in the visual and somatomotor ICs, functional connectivity to other ICs was decreased during task performance compared to resting state. These results are in line with those of Arbabshirani et al (2012), who found a general decrease in FNC during performance of an auditory oddball task compared to resting state. These authors suggested that performance of an active task may be facilitated by higher activation within specialized brain networks rather than collaboration between different networks. This idea is further supported by findings of Nir et al (2006). They compared visual stimulation to periods of eyes closed resting state and showed that during visual stimulation; functionally related visual areas were more strongly connected, while functionally dissimilar visual regions became de-correlated. Together with our results, this suggests that most networks show decreased connectivity to other functional networks with increasing levels of task demands.

As visual and somatomotor networks are essential for adequate performance in the selective attention and working memory tasks, it is puzzling why these networks showed a decrease as opposed to an increase in SEC during task performance compared to resting state. First of all, it should be noted that in the current study, participants closed their eyes during the resting state condition, while performance of the two tasks was dependent on the processing of visual input. This difference in visual input might have aggravated the observed effects of task compared to resting state on the SEC of visual ICs.

Alternatively, it might be the case that increases in SEC with increasing task demand are limited to those networks that play the most central role in the task. For example, working memory of visual items is thought to rely on the maintenance of sensory representations in the visual cortex as well as on the manipulation of these items. Therefore, especially areas involved in maintaining and manipulating this representation, such as the inferior frontal gyrus, would need to increase FNC during working memory tasks to enable adequate performance. A limitation of this study is that these two alternatives cannot be disentangled with this dataset. Future studies using an eyes open baseline period could investigate whether the observed FNC changes are truly related to task performance or to the difference between eyes open during task performance and eyes closed during resting state.

Our findings indicate an age-related difference in the modulation of FNC with condition. Whereas young participants show the maximal change in SEC patterns from less demanding to more demanding task conditions, older participants showed maximal change from rest to a low demanding task. It is important to note that this result cannot be due to the difference between eyes closed – eyes open in rest versus task, as there was no difference between older and younger adults in the comparison between resting state and the high demanding two-back task. This result fits well with previous literature on BOLD activation differences in elderly compared to young participants. In working memory studies, for example, it has been found that elderly show increased prefrontal activation compared to young participants in low working memory loads, whereas the opposite pattern is observed during high working memory loads (Mattay et al., 2006). According to Reuter-Lorenz and Cappell (2008), processing inefficiencies cause the aging brain to recruit more neural resources to achieve computational output equivalent to that of a younger brain. They argued that as demand increases, elderly can reach a resource ceiling (Grady, 2012). In turn this can lead to age-related declines in performance in more demanding tasks. In the context of the current results, the larger change in SEC patterns from resting state to the less demanding cognitive tasks in elderly compared to young adults, could reflect the recruitment of additional neural resources necessary to cope with task demands. The limited adaptation of centrality in case of additional task demands in elderly might be a sign of elderly reaching a resource ceiling. These results show that the theories of age-related change, mainly based on changes in brain activation, are in line with observed connectivity changes in the aging brain.

In addition, we observed that the functional connectivity to other ICs was larger in older compared to younger participants in a number of ICs (i.e. the visual ICs, the basal ganglia IC and the anterior cingulate IC). This age-related increase in connectivity between functional networks is in line with results from a previous study, in which we found that connectivity between functional networks was increased during a visual oddball task in older compared to younger participants (Geerligs et al., 2012a). Tomasi and Volkow (2012) also found indications that connectivity between functional networks increases with



age; they showed that long range connectivity from areas in the somatomotor network, thalamus and cerebellum was increased in elderly during resting state. Previous studies have demonstrated that besides increases in between network connectivity, connectivity within specific functional networks is decreased with age (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Grady et al., 2010; Rieckmann et al., 2011; Sambataro et al., 2010). Together, these age-related changes result in decreased segregation of functional networks. This is in line with the dedifferentiation theory of aging that suggests that areas in the older brain may become less functionally distinct (Baltes and Lindenberger, 1997; Carp et al., 2011a; Park et al., 2004). Moreover, it shows that dedifferentiation is not limited to brain areas but extends to functional networks as well (Geerligs et al., 2012a).

In four ICs, we found significantly different task dependent changes in centrality between older and younger participants (i.e. right FPCN, TPJ, somatosensory, and precuneus IC). In the right FPCN, younger participants showed increased centrality during the 2-back task compared to resting state and the SA task. This is well in line with expectations, as the main constituents of the right FPCN, the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex, are often found to be active during working memory tasks (Cabeza et al., 2008; Owen et al., 2005). However, in the elderly, the centrality of the right FPCN was not increased during performance of the 2-back task compared to resting state. In addition, the centrality was significantly smaller in older than younger participants in the 2-back task. Previous studies have demonstrated that the connectivity from the right DLPFC was decreased in elderly especially under conditions of high working memory load. Nagel and colleagues (2011), for example, showed that in young but not older participants, connectivity between the left and the right DLPFC increased with increasing working memory load. Furthermore, Rieckmann et al (2011) showed that functional connectivity from the right DLPFC to parietal areas and the occipitotemporal sulcus was reduced in older compared to younger participants during a working memory task. Implications of the reduced connectivity/centrality of the right FPCN in old relative to younger adults remains elusive at this moment. We, for example, did not observe a correlation between 2-back performance and SEC of this IC.

A second IC in which we observed task dependent changes of centrality between older and younger participants, was the TPJ. During the SA task, the centrality of the TPJ was increased in elderly compared to young participants. Whereas the dorsal parietal cortex is related to attentional top-down control, the TPJ plays an important role in the capture of bottom-up attention by an external stimulus (Cabeza et al., 2012; Corbetta and Shulman, 2002; Corbetta et al., 2008). Although older participants performed as accurate on this task as younger participants, we have shown in a previous study that older participants have trouble suppressing the information that is presented on the irrelevant spatial positions (Geerligs et al., 2012b). This is in line with a large body of research that has shown that elderly generally suffer more from distraction of irrelevant information than younger adults (see also: de Fockert et al., 2009; Gazzaley et al., 2005a; Gazzaley



et al., 2008; Haring et al., 2013; Hasher and Zacks, 1988; Hasher et al., 1999; Mager et al., 2007). Wen and colleagues (2012) showed that increased connectivity directed from the ventral attention network (including the TPJ), to the dorsal attention network, was associated with slower and less accurate performance in a visual spatial attention task. The increased centrality of the TPJ during the SA task might be related to an increased likelihood of attentional capture by (irrelevant) external stimuli in the elderly. However, as no direct link to performance was observed, it is important that this interpretation is tested in future studies.

Whereas most visual and somatomotor ICs showed a decrease in centrality in task performance compared to resting state, elderly showed an increase in the centrality in the somatosensory IC with increasing task demand. In younger participants there was no effect of task on somatosensory IC centrality. Similarly, in the precuneus IC (part of the DMN), centrality did not change between tasks in young participants while older participants showed a higher centrality in the 2-back task than in the SA task or resting state. Previous research has shown that older adults often have trouble with the suppression of activity as well as connectivity within the DMN, which is related to decreased task performance (Grady et al., 2006; Persson et al., 2007; Sambataro et al., 2010). Although we can only speculate about the more specific implications of the current findings, they do show that with age, the functional networks that are recruited for task performance change.

In this study we set out to study functional connectivity between networks and how the change in connectivity with changing task demands is affected by aging. It is important to note that the answer to this question heavily depends on the definition of networks. Here, we used independent component analysis to identify different brain networks. The recommended approach to use the minimal description length (MDL) procedure to find a suitable number of components resulted in a large number (38) of components (Li et al., 2007). Decomposing the data into these 38 components resulted in a quite regional decomposition, in which areas that are generally regarded as one functional network (e.g. the DMN) were split into subcomponents. This is in line with previous literature that has shown that functional networks can be identified at different levels of hierarchy (Meunier et al., 2009b; Meunier et al., 2010). It would be important for future studies to investigate whether these results would be similar when different methods are used to define functional networks.

In conclusion, elderly are able to adapt FNC to task demands. However, the impetus for FNC change is different in young and elderly. Whereas young participants showed the maximal shift in FNC patterns between the less demanding SA task and the more demanding 2-back task, older participants showed the maximal connectivity shift between resting state and the SA task. The observed increases in FNC from rest to task were found to be limited to those ICs that are involved in central functions related to the demands of the task at hand, whereas FNC decreases in the other ICs. We argued that the

age-related changes reflect the previously reported recruitment of additional resources in elderly.

#### 4.6 Supplementary material

Supplementary table 4.2 shows the results of the analysis procedure for two different significance thresholds. These results show that the general trends of increased SEC in older adults and general decreased SEC in task compared to resting state become even more pronounced when a less stringent threshold is used.

In addition, we examined the effect of regressing out the effects of stimulus presentation prior to computing the correlation matrix. Initially, variance associated with stimulus presentation was removed in the SA-task and the n-back task, to make sure that connectivity was not dominated by synchronized stimulus-evoked responses (Al-Aidroos et al., 2012; Geerligs et al., 2012a). However, we are interested in adaptations of connectivity to task demand. Therefore, removing the variance associated with stimulus presentation could have removed some effects of interest. Here, we repeated the original analysis without the removal of variance related to stimulus presentation. We found that the age-differences in changes in SEC patterns remained the same. In addition, the results of the repeated measures procedures were also highly similar compared to the analysis without removal of variance associated with stimulus presentation (see supplementary Table 4.3).

Supplementary table 4.1: Averages and standard deviation for the SEC, separately for each IC, task condition and age group

IC	Young			Old		
	rest	SA	2-back	rest	SA	2-back
1	1.11(0.27)	0.97(0.23)	1.01(0.28)	1.29(0.28)	1.15(0.24)	1.24(0.19)
2	1.01(0.3)	0.79(0.31)	0.99(0.29)	1.09(0.38)	0.97(0.22)	0.92(0.2)
3	1.04(0.33)	0.94(0.24)	1(0.24)	1.35(0.35)	1.05(0.23)	1.01(0.26)
4	1.27(0.27)	1.24(0.19)	1.11(0.26)	1.42(0.31)	1.27(0.22)	1.33(0.25)
5	1.3(0.2)	1.05(0.18)	1.13(0.27)	1.36(0.24)	1.18(0.2)	1.24(0.19)
6	1.11(0.31)	0.89(0.27)	1.01(0.3)	1.36(0.26)	1(0.34)	1.05(0.35)
7	1.23(0.3)	1.19(0.24)	1.03(0.32)	1.31(0.31)	1.13(0.24)	1.04(0.29)
8	1.21(0.34)	1.05(0.25)	0.95(0.3)	1.27(0.33)	1.03(0.3)	1.02(0.26)
9	1.23(0.25)	1.32(0.22)	1.21(0.28)	1.12(0.2)	1.24(0.23)	1.37(0.24)
10	1.08(0.28)	0.96(0.33)	1.14(0.23)	1.05(0.26)	1.05(0.3)	1.04(0.27)
11	1.14(0.36)	0.89(0.26)	1.11(0.26)	1.28(0.4)	1.05(0.29)	1.09(0.29)
12	1(0.34)	0.83(0.32)	0.94(0.24)	1.07(0.29)	0.99(0.23)	1.04(0.24)
13	0.87(0.27)	0.71(0.22)	0.77(0.23)	1.11(0.26)	1.02(0.26)	1.05(0.23)
14	1.06(0.22)	1.1(0.2)	0.97(0.27)	1.05(0.22)	1.07(0.23)	1.26(0.27)
15	0.87(0.32)	0.69(0.22)	0.88(0.29)	0.78(0.27)	0.77(0.22)	0.87(0.34)
16	1.13(0.23)	1.35(0.2)	1.18(0.25)	1.15(0.29)	1.08(0.25)	0.98(0.25)
17	0.77(0.27)	1.08(0.24)	0.88(0.26)	0.89(0.26)	0.99(0.23)	0.93(0.3)
18	1.18(0.29)	1.17(0.25)	1.1(0.24)	1.22(0.31)	1.05(0.26)	1.14(0.25)
19	1(0.37)	1(0.23)	1.29(0.2)	1.12(0.35)	1(0.29)	1.06(0.29)
20	1.03(0.23)	0.91(0.2)	0.94(0.28)	1.05(0.25)	0.95(0.27)	1.1(0.26)
21	1.09(0.24)	1.06(0.28)	0.92(0.25)	1.15(0.23)	0.92(0.26)	0.99(0.32)
22	0.84(0.26)	0.98(0.22)	1.24(0.23)	0.94(0.3)	1.06(0.23)	1.11(0.22)
23	1.01(0.29)	0.84(0.25)	1.1(0.23)	0.95(0.23)	1.17(0.25)	1.28(0.21)
24	1.16(0.26)	1.13(0.21)	1.23(0.25)	1.01(0.27)	1.21(0.17)	1.16(0.26)
25	0.91(0.22)	0.77(0.25)	0.79(0.24)	1.15(0.25)	1.08(0.19)	1.03(0.22)

Y=young, O=old, SA=selective attention task, 2B=2-back task, IC=independent component.

Supplementary table 4.2: Results of repeated measures analysis presented for different significance thresholds; effects of condition, age group and the interaction of age group and condition on SEC.

IC	Main effect task		Post-hoc			Main effect age		Post-hoc	Interaction task x age	
	F	p	RE>SA	R-2B	SA>2B	F	p	O>Y	F	p
Med. Visual (1)	7.23	0.004	RE>SA		2B>SA	19.6	<0.001	O>Y		
Lat. Visual (2)	5.98	0.007	RE>SA							
Ventral visual (3)	12.95	<0.001	RE>SA	RE>2B		9.81	0.011	O>Y	5.7	0.028
Dorsal visual (4)	4.95	0.020	RE>SA	RE>2B		10.27	0.009	O>Y		
Auditory (5)	19.28	<0.001	RE>SA	RE>2B	2B>SA	8.72	0.014	O>Y		
Somatomotor (6)	24.66	<0.001	RE>SA	RE>2B	2B>SA					
L. Somatomotor (7)	13.70	<0.001	RE>SA	RE>2B	SA>2B					
R. Somatomotor (8)	19.31	<0.001	RE>SA	RE>2B						
Somatosensory (9)	6.09	0.005	SA>RE	2B>RE					8.36	0.004
SMA (10)										
Paracentral lobule (11)	10.81	<0.001	RE>SA		2B>SA					
CB (12)	3.81	0.031	RE>SA			6.16	0.050	O>Y		
BG (13)	5.39	0.011	RE>SA			50.35	<0.001	O>Y		
Precuneus (14)									10.32	0.004
PCC (15)	4.81	0.016			2B>SA					
Med. Frontal (16)	5.49	0.010			SA>2B	16.49	<0.001	Y>O	6.36	0.016
Angular (17)	12.39	<0.001	SA>RE		SA>2B					
L. FPCN (18)										
R. FPCN (19)	7.58	0.002			2B>SA				7.74	0.007
L. AI/Operculum (20)	4.17	0.022	RE>SA		2B>SA					
R. AI/Operculum (21)	7.23	0.002	RE>SA	RE>2B						
Inf. Frontal (22)	24.67	<0.001	SA>RE	2B>RE	2B>SA				4.60	0.044
TPJ (23)	17.97	<0.001		2B>RE	2B>SA	13.67	<0.001	O>Y	12.95	<0.001
Med. Sup. Parietal (24)	4.80	0.016	SA>RE	2B>RE					4.45	0.044
Ant. Cingulate (25)	6.23	0.005	RE>SA	RE>2B		48.30	<0.001	O>Y		

Y=young, O=old, RE=rest, SA=selective attention task, 2B=2-back task, R=right, L=left, F=F-value, p=p-value, Ant=anterior, Inf=inferior, Sup=superior, Lat=lateral, Med=medial, SMA=supplementary motor area, CB=cerebellum, BG=basal ganglia, PCC=Posterior Cingulate Cortex, FPCN=fronto-parietal control network, AI=anterior insula, TPJ=temporoparietal junction, degrees of freedom for the F-test of the task effect and the interaction effect were 2 and 130, degrees of freedom for the F-test of the age effect were 1 and 65. Values in the white cells show results that are significant at  $p_{\text{fdr}} < 0.01$ , values in the shaded cells show results that are significant at  $p_{\text{fdr}} < 0.05$ .

## Flexibility of functional connectivity in the aging brain

Supplementary Table 4.3: Results of repeated measures analysis without removal of variance associated with stimulus presentation.

IC	Main effect task		Post-hoc			Main effect age		Post-hoc	Interaction task x age	
	F	p	RE-SA	R-2B	SA-2B	F	p	O>Y	F	p
Med. Visual (1)	8.86	0.002	RE>SA		2B>SA	14.12	<0.001	O>Y		
Lat. Visual (2)	10.81	<0.001	RE>SA		2B>SA					
Ventral visual (3)	13.56	<0.001	RE>SA	RE>2B		8.94	0.017	O>Y	5.57	0.028
Dorsal visual (4)	4.28	0.035		RE>2B		6.87	0.031	O>Y		
Auditory (5)	19.68	<0.001	RE>SA	RE>2B		8.33	0.020	O>Y		
Somatomotor (6)	24.23	<0.001	RE>SA	RE>2B	2B>SA	7.84	0.022	O>Y		
L. Somatomotor (7)	13.14	<0.001	RE>SA	RE>2B	SA>2B					
R. Somatomotor (8)	17.89	<0.001	RE>SA	RE>2B						
Somatosensory (9)	10.07	<0.001	SA>RE	2B>RE					7.33	0.009
SMA (10)										
Paracentral lobule (11)	15	<0.001	RE>SA	RE>2B	2B>SA					
CB (12)										
BG (13)	4.01	0.035	RE>SA	RE>2B		40.05	<0.001	O>Y		
Precuneus (14)									6.81	0.014
PCC (15)	6.23	0.007	RE>SA		2B>SA					
Med. Frontal (16)	6.41	0.006	SA>RE		SA>2B	9.60	0.016	Y>O	6.38	0.016
Angular (17)	13.54	<0.001	SA>RE		SA>2B					
L. FPCN (18)										
R. FPCN (19)	6.01	0.007			2B>SA				8.67	<0.001
L. AI/Operculum (20)	3.35	0.050	RE>SA							
R. AI/Operculum (21)	4.80	0.017	RE>SA	RE>2B					5.94	0.017
Inf. Frontal (22)	22.36	<0.001	SA>RE	2B>RE	2B>SA					
TPJ (23)	8.86	<0.001		2B>RE	2B>SA	14.21	<0.001	O>Y	11.44	<0.001
Med. Sup. Parietal (24)	3.39	0.050		2B>RE						
Ant. Cingulate (25)						35.56	<0.001	O>Y		

Y=young, O=old, RE=rest, SA=selective attention task, 2B=2-back task, R=right, L=left, Ant=anterior, Inf=inferior, Sup=superior, Lat=lateral, Med=medial, SMA=supplementary motor area, CB=cerebellum, BG=basal ganglia, PCC=Posterior Cingulate Cortex, FPCN=fronto-parietal control network, AI=anterior insula, TPJ=temporoparietal junction, degrees of freedom for the F-test of the task effect and the interaction effect were 2 and 130, degrees of freedom for the F-test of the age effect were 1 and 65. Values in the white cells show results that are significant at  $p_{\text{fdr}} < 0.01$ , values in the shaded cells show results that are significant at  $p_{\text{fdr}} < 0.05$ .



# Chapter 5

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An EEG study on the neural correlates of suppression of irrelevant information in old and young

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## 5 An EEG study on the neural correlates of suppression of irrelevant information in old and young

### 5.1 Abstract

With increasing age, people experience more difficulties with suppressing irrelevant information, which may have a major impact on cognitive functioning. The extent of decline of inhibitory functions\* with age is highly variable between individuals. In this study we used event related potentials and phase locking analyses to investigate neural correlates of this variability in inhibition between individuals.

Older and younger participants performed a selective attention task in which relevant and irrelevant information was presented simultaneously. The participants were split into high and low performers based on their level of inhibition inefficiency, that is, the slowing of response times induced by information participants were instructed to ignore. P1 peak amplitudes were larger in low performers than in high performers, indicating that low performers were less able to suppress processing of irrelevant stimuli.

Phase locking analyses were used as a measure of functional connectivity. Efficient inhibition in both age groups was related to increased functional connectivity in the alpha band between frontal and occipito-parietal ROIs in the prestimulus interval. In addition, increased power in the alpha band in occipito-parietal ROIs was related to better inhibition both before and after stimulus onset. Phase locking in the upper beta band before and during stimulus presentation between frontal and occipito-parietal ROIs was related to better performance in elderly only, suggesting that this is an active compensation mechanism employed to maintain adequate performance. In addition, increased top-down modulation and increased power in the alpha band appears to be a general mechanism facilitating inhibition in both age-groups.

### 5.2 Introduction

Studies investigating how aging affects visual selective attention and inhibition have shown that the elderly have problems suppressing irrelevant information, while there are no evident problems in their ability to process relevant information (de Fockert et al., 2009; Gazzaley et al., 2005a; Gazzaley et al., 2008; Mager et al., 2007; but see Wild-Wall et al., 2008). According to the inhibitory deficit theory (Hasher & Zacks, 1988), this deficit in inhibition may have an influence on performance in a range of attention and memory tasks (for recent confirmation see Gazzaley et al., 2005a). However, there are studies showing that the deficits in inhibition processes with age are not unitary in nature and are not found in all tasks (Kramer et al., 1994).

Less efficient suppression of irrelevant information in the elderly has been linked to a deficit in top-down modulation of early visual processing stages (Gazzaley et al., 2008). Top down modulation is crucial for our ability to voluntarily focus on relevant information and ignore irrelevant information in accordance with task instructions, expectations or goals. Top down control is thought to be actualized through enhancement of activity in cortical areas processing relevant information and suppression of activity in cortical areas processing irrelevant information (Pinsk et al., 2004). These mechanisms underlying visual selective attention have been related to a neural network consisting of dorsal parietal and frontal brain areas (Corbetta & Shulman, 2002; Miller & D'Esposito, 2005; Noudoost et al., 2010). Recent research in monkeys using implanted electrodes has corroborated these results, and in addition showed that top-down control is initiated in the frontal cortex, while activity in parietal areas is affected in a later stage of processing (Buschman & Miller, 2007). The communication between distant regions such as frontal and parietal areas is reflected in phase locking of their oscillatory activity (Fries, 2005; Sauseng & Klimesch, 2008).

In ERP studies, reduced top-down suppression of irrelevant information has been linked to increased amplitude of early ERP components, such as the P1 (Zanto & Gazzaley, 2009) and N170 (de Fockert et al., 2009). In a working memory task, for example, young participants showed a reduction in P1 amplitude when irrelevant images were presented during task performance, compared to viewing the same images with no accompanying task. The elderly did not show this reduction, which was interpreted as evidence that this group was unable to suppress irrelevant information during task performance (Zanto & Gazzaley, 2009).

Top-down suppression of irrelevant information has also been linked to an increase in EEG alpha power in young participants (Freunberger et al., 2008). When young participants received information in advance about the location of an upcoming target, alpha power was larger in the hemisphere ipsilateral to the target than in the hemisphere contralateral to the target. This indicates that participants prepared for the upcoming stimulus by suppressing visual processing activity at irrelevant spatial locations. These findings are consistent with those of studies investigating working memory and long term memory performance, showing that increased alpha power in task-irrelevant regions was predictive of good performance (Haegens et al., 2010; Meeuwissen et al., 2011).

The prefrontal cortex (PFC), implicated in inhibition of irrelevant sensory information (Aron et al., 2004; Knight et al., 1999), is one of the areas showing the greatest atrophy with age (Raz et al., 2005). Thus, structural decline in this brain area might be responsible, at least partly, for the inhibitory deficit in elderly. However, according to the scaffolding theory of aging (Park & Reuter-Lorenz, 2009) enhanced activity in frontal areas is a hallmark of the brain's adaptation to a range of neural challenges it faces during the life span. The

theory posits that, despite functional deterioration, an adequate performance level in elderly is maintained due to engagement of additional neural circuitry. The additional circuitry is suggested to primarily involve frontal brain areas; however, parietal, temporal or occipital areas might be included, as well.

It is important to note that studies of aging often have treated the elderly as a homogeneous group, assuming the same general pattern of cognitive decline in all individuals (Colcombe et al., 2005; for exceptions see Daffner et al., 2011; Duverne et al., 2008; Nagel et al., 2009). However, large individual differences have been observed within the elderly population (Park & Reuter-Lorenz, 2009). In view of the need to develop interventions to slow age-related changes in performance (e.g., cognitive training methods, adaptations of work environment), it is of great importance to understand why some older individuals are able to maintain their level of cognitive function into old age, while others cannot. The main aim of the present study is to examine age-related changes in processing of relevant and irrelevant information using both behavioral and electrophysiological indices of performance, taking into account differences between high and low performing individuals.

Inhibition was measured using a selective attention task, in which relevant and irrelevant information could be presented simultaneously. Participants were instructed to press 'yes' when a target letter was presented on one of the relevant positions on the screen and press 'no' in all other cases. An inhibition inefficiency score was derived by assessing how response times were affected by a target letter presented on one of the irrelevant locations on the screen compared to trials in which no target letters were presented. Based on previous research, we hypothesized that an individual's ability to inhibit irrelevant information would be related to the amplitude of the P1 ERP component (Gazzaley et al., 2008). In addition we expected an increase in functional connectivity between signals measured at frontal and occipito-parietal electrode locations, as reflected in higher phase locking values in the alpha band, in individuals with a high ability to inhibit irrelevant information compared to those who have a lower ability to inhibit irrelevant information.

### 5.3 Methods

#### 5.3.1 Participants

Forty-four older adults (20 males,  $M_{\text{age}} = 65.8$  years, age range: 60-74 years) and 40 younger adults (20 males,  $M_{\text{age}} = 19.8$  years, age range: 18-26 years) participated in this experiment. All participants were right handed and had no history of neurological or psychiatric disorders. Older participants had a score above 26 on the Mini Mental Status Examination (MMSE, Folstein et al., 1975) and below 16 on each of the subscales of the

Hospital Anxiety and Depression Scale (HADS, Zigmond & Snaith, 1983). All participants had normal or corrected-to-normal visual acuity. The study adhered to the Declaration of Helsinki and was approved by the local ethics committee. Informed consent was obtained from all participants.

### 5.3.2 Stimuli and apparatus

The task used in the current experiment was a modified version of the selective attention task used by Wijers et al. (1987). In this version of the task (figure 5.1), an experimental block started with the presentation of the target letter, followed by the presentation of a cue frame, indicating which diagonal (right-up, left-up, horizontal) was relevant. Both the target letter and the cue frame were presented for 5000 ms. After the instruction, a series of 150 trials was presented in each block. In each trial the stimuli were presented for 300 ms followed by an inter-stimulus interval varying randomly between 2000 and 2500 ms. A fixation cross in the middle of the screen remained visible throughout a block of trials.

Participants were required to pay attention to information presented on the relevant diagonal and to ignore information presented on the irrelevant diagonals. For half of the participants a right hand index finger response was required if a target letter appeared on a relevant diagonal position (relevant target) and a right hand middle finger response was required in all other conditions (i.e., target letter on irrelevant diagonal positions (irrelevant target) or no target letter presented on the relevant diagonal (non-target)). For the other half of the participants index and middle finger responses were reversed. Relevant target trials made up 25% of the total number of trials. There were never two target letters present in one trial. In addition display load was varied; the stimulus display contained 2, 4 or 6 letters. On diagonals where no letters were displayed masks were presented to keep the amount of visual input similar over conditions. The display load manipulation will not be discussed in the current paper. The outcome measure of interest in this task was the ability to inhibit irrelevant information on the screen. This was measured by the difference in median reaction time between irrelevant target trials and non-target trials, averaged over the other task variations such as display load and whether or not letters were presented on the relevant diagonal. This difference score is referred to as the inhibition inefficiency score.

Stimuli were presented on a Pentium IV PC, equipped with a 17 inch monitor. Stimulus generation and response collection were controlled using E-prime 1.2. All stimuli were white on a black screen in font Arial, size 18. Stimulus letters were randomly chosen from the alphabet, excluding the letters g, i, o, q, u, x and y. The visual angle from the centre of fixation to each of the letters was  $2.3^\circ$  with a viewing distance of 75 cm. In total, there were 6 blocks of 150 stimuli. Between every two blocks, there was a two-minute break to avoid effects of mental fatigue due to prolonged task performance.

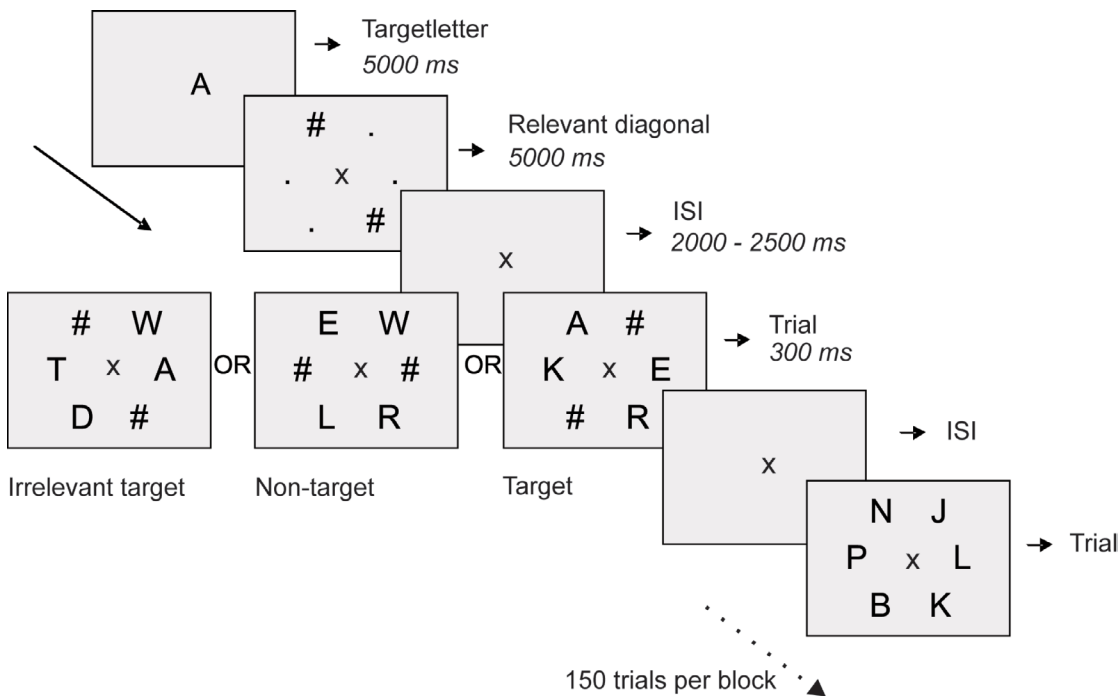


Figure 5.1: Schematic overview of different task conditions

### 5.3.3 Procedure

The experiment consisted of 2 sessions carried out on separate days. In the first session participants performed a series of neuropsychological tests, which were used to check whether differences between groups in the inhibition task were related to speed of information processing or intelligence. The test battery included the Dutch Adult Reading Test (Schmandt et al., 1992), the WAIS III digit span, digit symbol and matrix reasoning tests (Uterwijk, 2001) and a simple reaction time test (see Table 5.1). Visual acuity was measured using reading charts at a distance of 75 cm; a score of 1 reflects normal visual acuity. Additionally, participants practiced the selective attention task in three blocks of 50 trials. During the training, feedback on performance levels was given after each block. In the second session, participants performed the selective attention task while EEG was measured.

### 5.3.4 Performance level split

To examine the relation between individual differences in inhibition and brain activity, both the older and the younger groups were split into high and low performers. The split was based on the inhibition inefficiency score; the difference in median reaction times between trials in which a target was presented on an irrelevant location and trials in which no target letters were presented. Participants with an inhibition inefficiency score smaller than the median in their age group were considered to be high performers, those with a score above the median as low performers. Participants with an inhibition inefficiency

score higher or lower than two standard deviations from the group mean were excluded from the analysis to prevent artificial inflation of correlations. This led to the removal of four outliers, two younger participants and two older participants.

### 5.3.5 EEG measurement and data analysis

EEG was recorded using 64 tin electrodes attached to a cap (ElectroCap International Inc., Eaton, Ohio, USA). The electrodes were placed at sites specified by the international 10-10 system (except F1, F2, CP1, CP2, FT7 and FT8). A REFA 8-72 amplifier (Twente Medical, Systems, Enschede, The Netherlands) was used to sample the signal at 500 Hz, with a low pass filter of 135 Hz (48 dB/oct). The Electro-Oculogram (EOG) was recorded bilaterally from electrodes placed at the outer canthi of both eyes and above and below the left eye. Data acquisition was performed using Brain Vision Recorder (version 1.03, BrainProducts GmbH, Munich, Germany).

Preprocessing of the data was executed using Brain Vision Analyzer (version 1.05, BrainProducts GmbH, Munich, Germany). Trials with incorrect responses were excluded from analysis. Data were down-sampled to 250 Hz, re-referenced to the average of the mastoid electrodes and filtered with a high pass filter of 0.16 Hz. For time frequency analysis, a low pass filter of 55 Hz (48 dB/oct) was used. A low-pass filter of 40 Hz (24 dB/oct) was used for the ERP analysis. Ocular correction was applied using the algorithm of Gratton, Coles and Donchin (1983). No horizontal eye movements were observed in relevant segments. Segments for ERP analysis ranged from -200 to 1000 ms around stimulus onset and baseline correction was applied to the pre-stimulus interval from -200 to 0 msec. Segments for the phase locking analysis ranged from 1 s pre-stimulus to 1 s post-stimulus. For the ERP analysis, trials were considered artifacts when the difference between the highest and the lowest voltage within a segment at PO7 or PO8 was more than 200  $\mu$ V and when there was a difference larger than 50  $\mu$ V between subsequent data points. For the time-frequency analysis, trials were considered artifacts when there was a difference larger than 75  $\mu$ V between subsequent data points on one of the channels involved in the analysis. The number of trials considered as artifacts did not differ significantly between high and low performing participants. After the exclusion of artifacts and incorrect trials, an average of 817 trials remained for subsequent analysis.

To calculate phase locking values between different frontal and occipito-parietal regions of interest (ROIs), the Fieldtrip toolbox for EEG/MEG-analysis was used (Oostenveld et al., 2011). The choice for particular ROIs was partly based on previous research (Zanto et al., 2010) and extended with frontal ROIs, as it has been suggested that inhibition and selective attention involves a widespread frontoparietal network (Pinsk et al., 2004). Except for the central frontal ROI (average of 3 electrodes: AFz, Fz and FCz), all ROIs were averages of the signals measured at 5 electrodes: FC1, FC3, FC5, C3, F3 (left frontal), FC2,



FC4, FC6, F4, C4 (right frontal), P3, P5, P7, PO3, PO7 (left occipito-parietal), POz, Oz, O1, O2, Iz (central occipito-parietal), and P4, P6, P8, PO4, PO8 (right occipito-parietal).

Time frequency analyses and phase computations were performed using Morlet wavelets (family ratio:  $f_0/\sigma_f=7$ ) in three frequency bands: the alpha band (8-12 Hz), the lower beta band (13-20 Hz) and the upper beta band (21-30 Hz). These frequency bands were based on previous research (Sauseng & Klimesch, 2008), indicating that long range connectivity in alpha and beta waves plays a role in inhibition and attention processes. Phase locking values (PLV) were computed by measuring the inter-trial variability of the difference in phase between two ROIs at each time-frequency point (Lachaux et al., 1999). This procedure results in a measure between 0 and 1, where 0 represents a random phase difference and 1 represents a constant phase difference. In addition to PLV, the power values, as computed by the Morlet wavelets, were examined to check for artificial differences in PLV, induced by power differences. Averages of the phase locking and power values were computed in four 200 ms intervals, ranging from 400 ms before stimulus onset to 400 ms after stimulus onset. Due to the Morlet wavelet procedure, the PLV and power values at each time point are estimates based on a range of time points encompassing seven cycles of the frequency of interest. Data of five participants were removed from the PLV and power analysis because of bad data quality for one of the electrodes within one of the ROIs.

### 5.3.6 Data Reduction and Statistical Analyses

Based on findings in previous studies, where the P1 and N1 were linked to inhibition of irrelevant information, we specifically looked at these ERP components (Gazzaley et al., 2005b). P1 peak amplitude was quantified as the most positive value between 50 and 150 ms after stimulus onset at PO7 and PO8, the N1 as the most negative value between 120 and 220 ms at PO7 and PO8. Data from one participant were excluded from the ERP analysis because of bad signal quality at electrode PO8. Analysis of behavioral data, ERP peak amplitudes and latencies was performed using mixed effects ANOVAs. Within subject factors were task condition and electrode (only for the analysis of ERPs), between subject factors were age group, performance level (high/low) and the interaction between age and performance level. To check whether the behavioral results were confounded by effects of processing speed, two different measures of processing speed, reaction time in the reaction time task and response time in non-target trials, were used as covariates in two separate ANCOVAs. Planned comparisons and post hoc-tests were performed using t-test. For the t-tests, corrections for unequal variances were applied when required. All correlation analyses (between phase locking, P1 amplitude and inhibition inefficiency scores) were performed using one sided Spearman rank correlations. The Spearman rank correlation coefficient was used instead of the Pearson correlation coefficient to cope with deviations from normality, linearity and to reduce effects of possible outliers.



To assess whether correlations were significantly different in the older and the younger groups, a Monte Carlo resampling procedure was used. Participants were randomly assigned to one of two groups. Within each group the correlation was computed, and subsequently the difference between the correlations in the groups was stored. This procedure was repeated 5000 times to generate a null distribution. Only when the difference in the correlations between the older and the younger groups was larger than the largest 5% of this null distribution, we concluded that the correlations were significantly different between the age groups and we calculated separate Spearman rank correlations. The effect of age on phase locking values and power values was computed using the Mann-Whitney U test, a non-parametric alternative for the t-test. This test was used instead of the t-test to reduce effects of outliers and to cope with non-normal data. The standard effect size of the Mann-Whitney U test ( $r$ ) was computed by dividing the z-value by the square root of the number of participants in the analysis. The significance level was set at  $p=0.05$ .

For the analysis of phase locking values, each time frequency bin contained 15 comparisons (electrode-pairs), for the analysis of power values there were 6 comparisons (electrodes) in each bin. Monte Carlo resampling procedures were used to evaluate the probability of the observed number of significant effects in each time frequency bin (similar to the procedure used by Hanslmayr et al., 2007). The scores of participants were randomly exchanged, and correlations or group differences within a time-frequency bin were computed. The number of significant ( $p<0.05$ ) effects was stored. This procedure was repeated 5000 times to generate a null distribution. When the actual number of significant results was larger than the cut-off number corresponding to the largest 5% of this null distribution, we concluded that the number of significant differences was larger than could be expected based on chance. In the figures, we indicated whether results in a given time-frequency bin were found significant according to this procedure by adding an asterisk. Only results that were significant according to this procedure were presented in the results section.

## 5.4 Results

### 5.4.1 Behavioral data

The inhibition inefficiency score measures the extent to which participants were affected by irrelevant information. A median split on the inhibition inefficiency score was used to categorize participants into high and low performers (see Methods). As accuracy levels for both conditions were almost at ceiling level ( $>99\%$  accuracy), the split only incorporated differences in response times. In all groups the inhibition inefficiency score was significantly larger than zero ( $t(18/19)=6.6-25.1, p<0.0005$ ). The inhibition inefficiency

score was larger for older than for younger participants ( $F(1,74)=15.1, p<0.0005$ ). However, this difference depended on performance level ( $F(1,74)=8.4, p=0.005$ ), that is, old high performers ( $M=7.5, SD=5.1$ ) and young high performers ( $M=6.4, SD=3.6$ ) did not differ, while old low performers had a significantly higher inhibition inefficiency score ( $M=24.7, SD=6.6$ ) than young low performers ( $M=17.3, SD=3; t(26.9)=-4.5, p<0.0005$ ).

ANCOVAs were used to control for the effects of processing speed on the inhibition inefficiency score. Both reaction times as measured with the simple reaction time test and response times in non-target trials were entered as covariates of no interest. Effects of performance level and the age by performance interaction did not change. The effects of age group remained significant when adding the response time in non-target trials ( $F(1,73)=6.9, p=0.01$ ) or the reaction time in the reaction time test ( $F(1,73)=9.7, p<0.003$ ) as covariates.

No differences were observed between high and low performers in average response times for any of the task conditions ( $F(1,74)=0.39, n.s.$ ), nor did high and low performers differ on scores for the simple reaction time test ( $F(1,73)=-0.21, n.s.$ ), Dutch reading test IQ ( $F(1,74)=-0.99, n.s.$ ) or WAIS matrices IQ ( $F(1,74)=0.01, n.s.$ ). In addition, none of the neuropsychological tests showed an age by performance interaction. Younger participants scored significantly better than older participants on tests for speed of information processing and visual acuity (Table 5.1). No age differences in IQ score were found, indexed by the WAIS matrices test, while the Dutch Reading test, a test of crystallized intelligence, showed significantly better performance for older than for younger participants.

Table 5.1: Neuropsychological, demographic and experimental variables

	Young HP	Young LP	Old HP	Old LP
Sex (m/f)	11/8	9/10	9/11	10/10
Age (years)	19.6 (1.2)	20.2 (2.2)	65.6 (4.3)	65.6 (3.9)
Visual acuity <sup>1</sup>	1.1 (0.1)	1.0 (0.2)	0.8 (0.2)	0.8 (0.1)
Dutch Reading test IQ <sup>1</sup>	101 (4)	102 (6)	107 (8)	110 (12)
WAIS Matrices IQ	110 (8)	111 (11)	108 (11)	107 (11)
Digit Symbol <sup>1</sup>	87 (11)	85 (14)	67 (11)	62 (15)
Reaction time test (ms) <sup>1</sup>	219 (20)	220 (22)	236 (18)	240 (34)
RT non-target trials (ms) <sup>1</sup>	399 (56)	416 (61)	567 (71)	561 (70)
Inhibition inefficiency (ms) <sup>23</sup>	6.4 (3.6)	17.3 (3)	7.5 (5.1)	24.7 (6.6)
P1 amplitude ( $\mu V$ ) <sup>2</sup>	3.2 (1.5)	3.7 (1.6)	3 (1.9)	5.4 (3.4)

Numbers represent mean (standard deviation). m: male; f: female; 1: significant difference between old and young participants ( $p<0.005$ ). 2: significant difference between high and low performers ( $p<0.01$ ). 3: significant interaction between age and performance level ( $p<0.005$ )

### 5.4.2 ERP data

The results for the P1 peak matched the pattern we found for the behavioral data; in the low performing elderly group P1 amplitude ( $M=5.4$ ,  $SD=3.4$ ) was larger than in the other groups (performance level  $F(1,73)=8.7$ ,  $p=0.004$ ). Additionally, low performing younger participants showed a slightly larger P1 ( $M=3.7$ ,  $SD=1.6$ ) than both young ( $M=3.2$ ,  $SD=1.5$ ) and old high performing participants ( $M=3$ ,  $SD=1.9$ ; see figure 5.2).

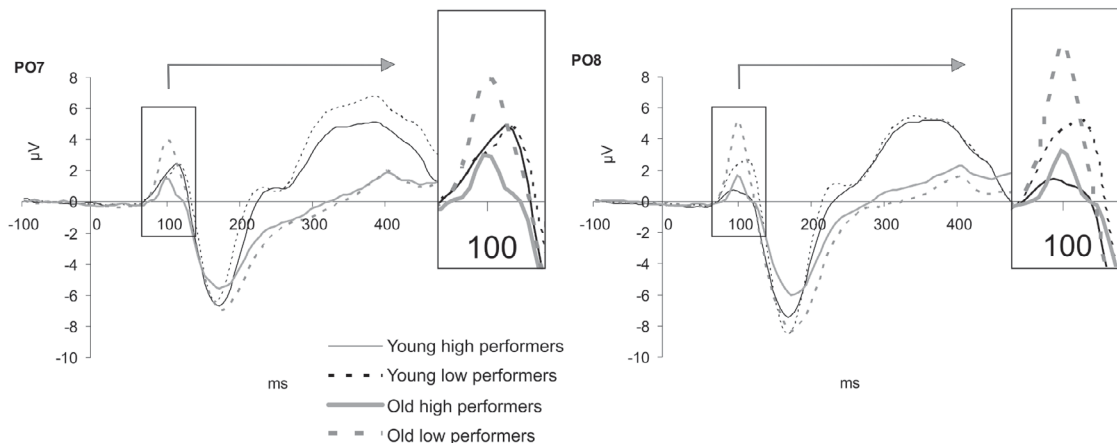


Figure 5.2: ERP waveforms at electrodes PO7 and PO8 illustrating the P1 component. The waveform is averaged over all task conditions and superimposed for age and performance level.

P1 amplitude differences between high and low performers were more pronounced at the right hemisphere electrode (PO8) than at the left hemisphere electrode (PO7) (performance level\*electrode:  $F(1,73)=5.4$ ,  $p=0.022$ ). Correlation analyses revealed that P1 amplitude correlated significantly with the inhibition inefficiency score at PO8 ( $r=0.342$ ,  $p=0.001$ ), that is, participants with a larger inhibition inefficiency score had larger P1 amplitudes (see figure 5.3). However, this correlation was not present at PO7. Monte Carlo resampling procedures revealed that correlations between P1 amplitude and inhibition inefficiency score did not differ significantly between the older and the younger group. There was no effect of trial type (target/non-target/irrelevant target) on P1 or N1 amplitude. No effects of age or performance level or condition on N1 amplitude or P1 and N1 latency were observed.

### 5.4.3 Phase locking

Connections between the different ROIs were examined in the phase locking analysis to identify correlations with the inhibition inefficiency score and P1 amplitude as well as differences between age groups. In figure 5.4 and 5.5 the significant results are summarized for both the alpha and beta frequency bands. When the number of significant results for a specific time-frequency bin exceeds the number expected by chance, this is indicated by an asterisk in the figure and these results are described in the results section.

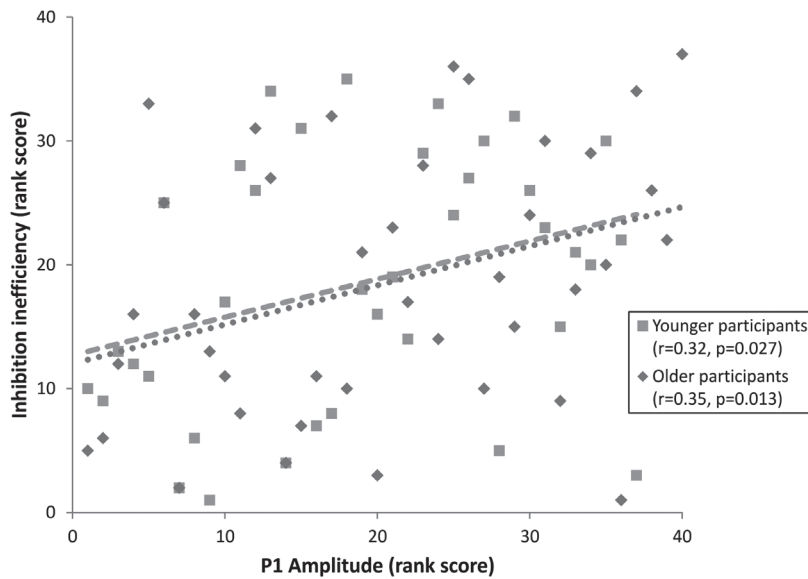
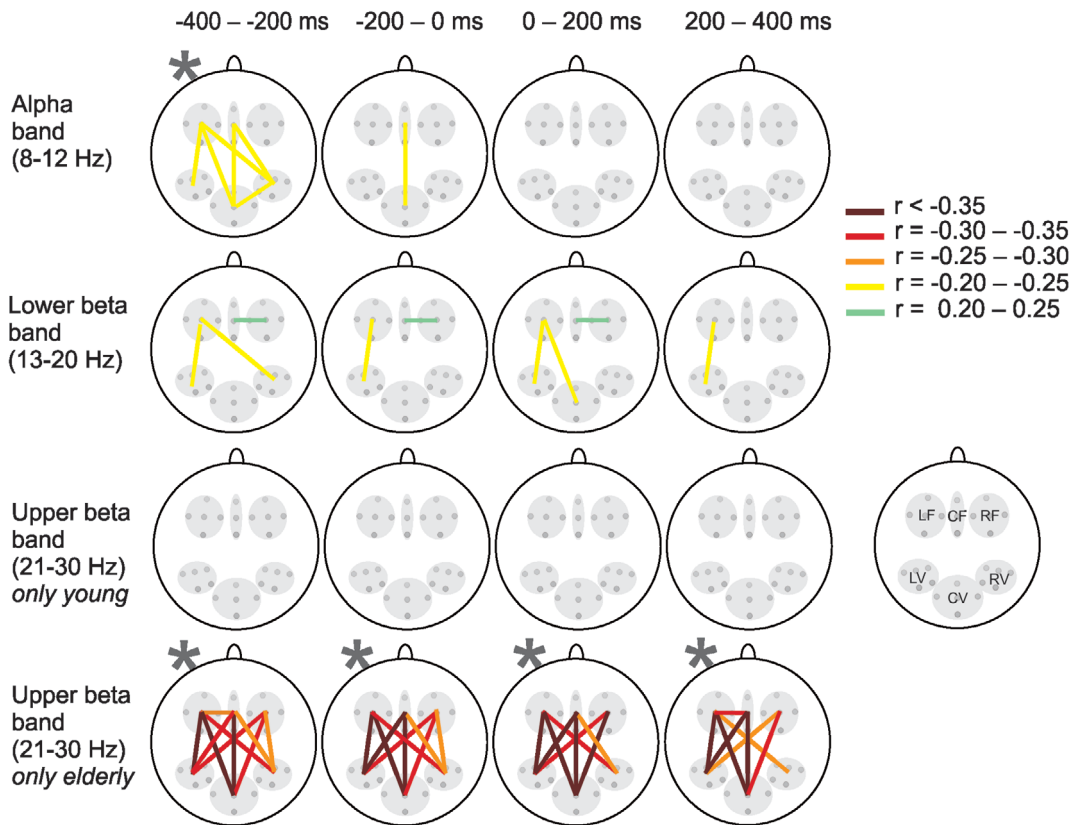


Figure 5.3: Correlation between P1 amplitude at electrode PO8 and inhibition inefficiency. Because the non-parametric Spearman rank correlation was used, rank scores are shown.

Phase locking in the alpha band (8-12 Hz) between frontal and occipito-parietal ROIs consistently correlated negatively with the inhibition inefficiency score in the first interval before stimulus onset (i.e. -400 - -200 ms). Participants with a higher ability to inhibit irrelevant information (lower inhibition inefficiency score) showed more phase locking between frontal and occipito-parietal ROIs (see figure 5.4a). Correlations did not differ significantly between the older and the younger group. Age effects in the alpha band were mainly limited to post-stimulus stages of stimulus processing; older participants showed more phase locking in the alpha band between frontal and occipito-parietal ROIs than young participants between 200 - 400 ms after stimulus presentation.

Effects of age on PLV in the lower beta band (13-20 Hz) were present in all time intervals, although the differences between age groups were only significant after correction for multiple comparisons in the intervals after stimulus onset. Elderly showed larger phase locking values between frontal and occipito-parietal ROIs than young participants, while phase locking was reduced between frontal ROIs for elderly compared to young participants (see figure 5.4b). Correlations between P1 amplitude and phase locking in the lower beta band differed across age groups. In older participants the P1 amplitude decreased with increased phase locking between frontal and occipito-parietal ROIs (over all intervals), while in young participants the effects did not reach the level of corrected significance.

a) Correlations between PLV and inhibition inefficiency scores



b) Differences between young and older participants in PLV

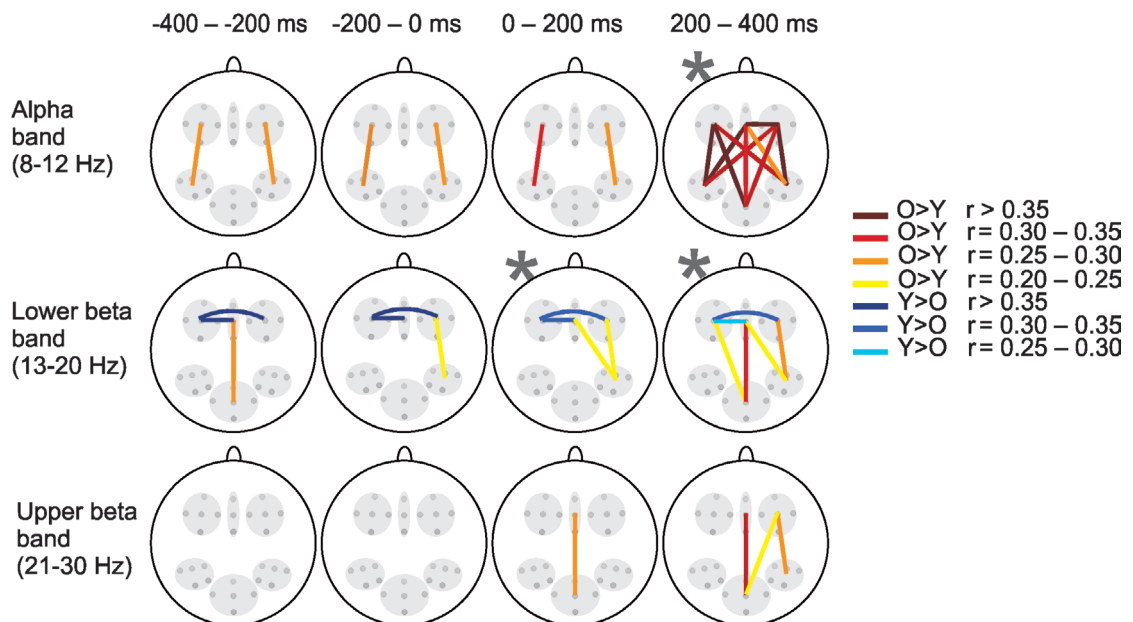


Figure 5.4: **A** Significant correlations ( $r$ ;  $p < 0.05$ ) between phase locking values in different ROIs and the inhibition inefficiency (pooled over the two age groups). Line color indicates strength and sign of the correlation. Note: In the upper beta band, correlations are presented separately for the younger and elderly groups because interactions between age group and inhibition inefficiency were observed in this frequency band. An asterisk (\*) indicates that the number of

significant correlations or group differences in that time-frequency bin exceeds the number expected by chance ( $p < 0.05$ ). The lower right head model shows the names abbreviated names associated with the different ROIs; left occipito-parietal (L-OP) central occipito-parietal (C-OP), right occipito-parietal (R-OP), left frontal (LF), central frontal (CF) and right frontal (RF). **B** Significant differences between age groups ( $p < 0.05$ ) in phase locking values between different ROIs. Line color indicates effect size ( $r$ ) and sign of the difference.

In the higher beta band (21-30 Hz) the Monte Carlo resampling procedure showed that the correlation between phase locking values and inhibition inefficiency scores was significantly different in the older and the younger groups. While no correlations were observed between the inhibition inefficiency score and phase locking in the young group, higher phase locking values between frontal and occipito-parietal ROIs in the elderly were correlated with more efficient inhibition over all time intervals. Also the correlations between the P1 amplitude and phase locking in the upper beta band were significantly different between age groups. Younger participants showed no significant correlations while elderly showed a smaller P1 amplitude with increased frontal to occipito-parietal and occipito-parietal to occipito-parietal phase locking (over all intervals). These correlations were stronger than those in the lower beta band.

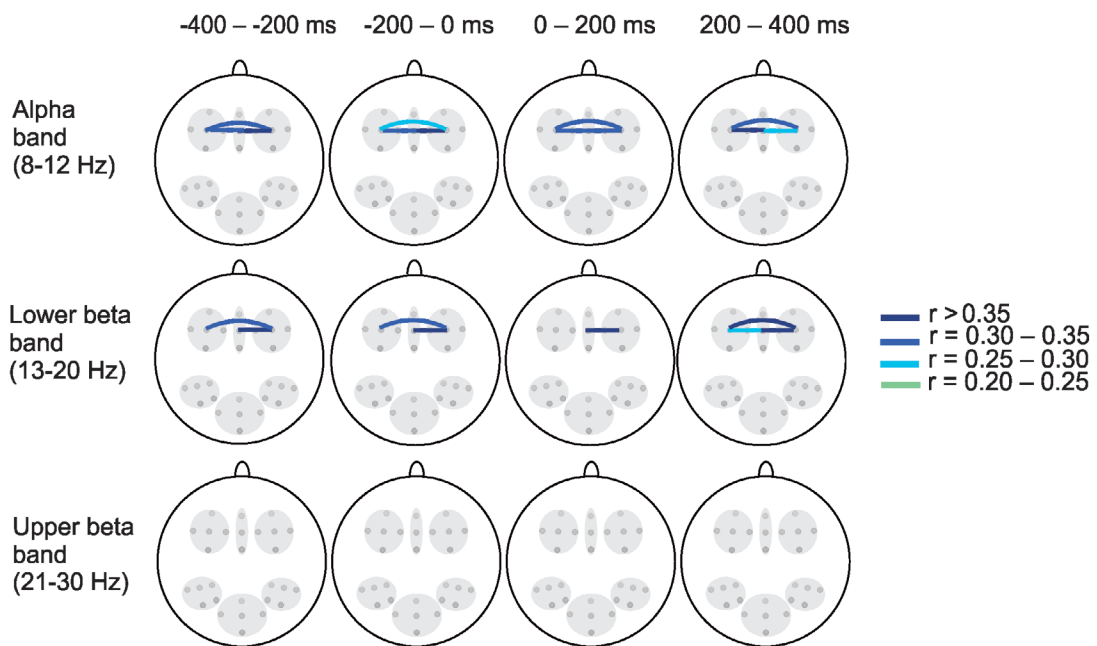
Because phase locking in both the alpha and the upper beta band correlated with inhibition inefficiency scores in older participants, we additionally computed the correlation between the average frontal to occipito-parietal phase locking in the alpha band (-400 - -200 ms) and phase locking in the upper beta band (see figure 5.6). There was a significant interaction between young and older participants. In younger participants, there was no correlation between alpha and upper beta phase locking. Older participants with higher alpha phase locking also showed increased upper beta phase locking, this effect was mainly present between frontal and occipito-parietal ROIs but also between occipito-parietal ROIs and between frontal ROIs (over all intervals).

Additional analyses of differences in absolute power levels revealed that older participants had less power in the alpha band in the right and central occipito-parietal ROIs than young participants over all intervals (significant between 0 and 400 ms, see figure 5.7b). Older participants had increased power in left and right frontal and left occipito-parietal ROIs in the lower beta band. Moreover, in the higher beta band older participants had more power than young participants in all frontal ROIs and in the left occipito-parietal ROI in pre- and post-stimulus intervals.

In both younger and older participants, power in the alpha band at occipito-parietal ROIs correlated with the inhibition inefficiency score. Participants with more power in the alpha band were better at inhibiting the irrelevant information on the screen (see figure 5.7a). Correlations between power and inhibition inefficiency were not significantly different for the two age groups. There were no significant correlations between power and P1 amplitude.



a) Correlations between PLV and P1 in young participants



b) Correlations between PLV and P1 in older participants

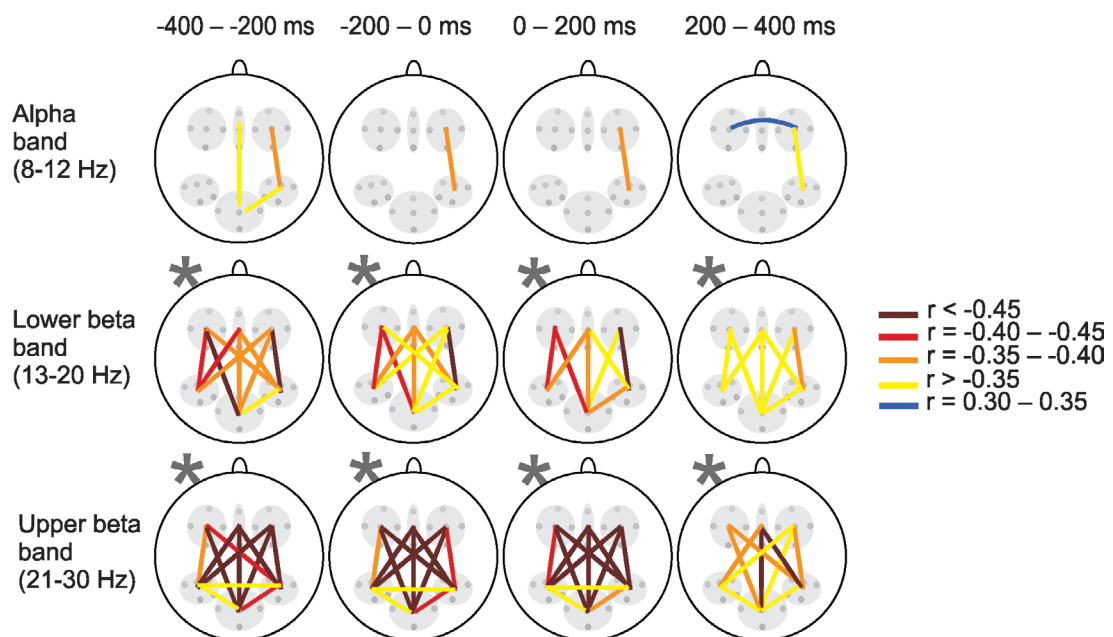


Figure 5.5: Significant correlations ( $r$ ;  $p < 0.05$ ) between phase locking values in different ROIs and the P1 amplitude in the a) younger and the b) older group. Note: correlations are presented separately for the younger and elderly groups because interactions between age group and P1 amplitude were observed in all frequency bands. Line color indicates effect size ( $r$ ) and sign of the difference. An asterisk (\*) indicates that the number of significant correlations in that time-frequency bin exceeds the number expected by chance ( $p < 0.05$ ).



Correlations between average alpha PLV (-400 - -200 ms) and upper beta PLV

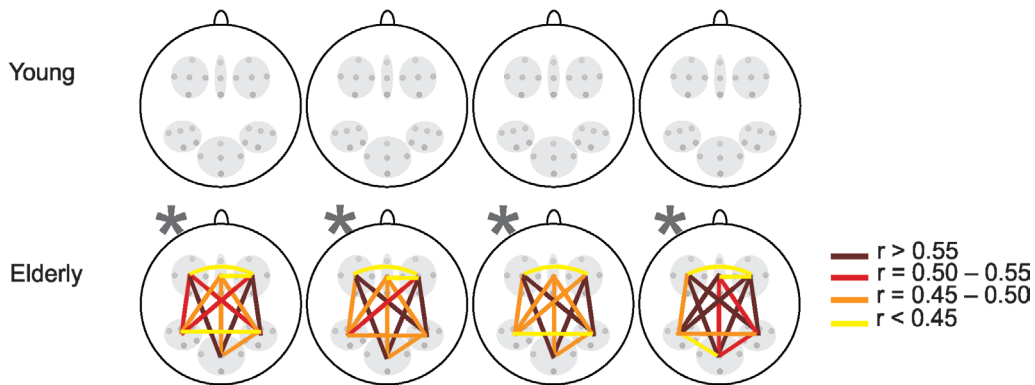
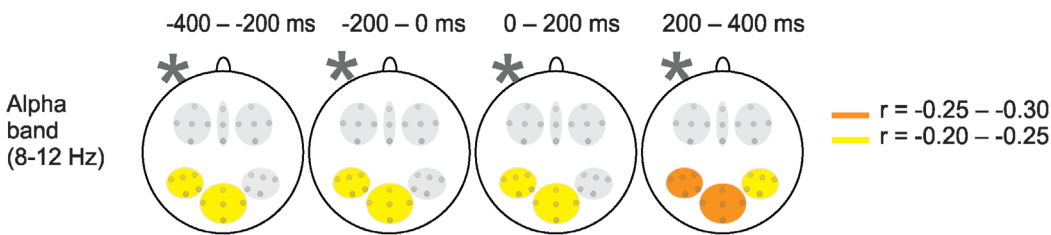


Figure 5.6: Significant correlations ( $r$ ;  $p < 0.05$ ) between the average fronto-parietal phase locking value in the alpha band (-400 - -200 ms) and phase locking values in the upper beta band, separately for the older and the younger groups. Note: correlations are presented separately for the younger and elderly groups because interactions between age group and average fronto-parietal phase locking value in the alpha band were observed. Line color indicates effect size ( $r$ ) and sign of the difference. An asterisk (\*) indicates that the number of significant correlations in that time-frequency bin exceeds the number expected by chance ( $p < 0.05$ ).

a) Correlations between power and inhibition inefficiency scores



b) Differences between young and older participants in power

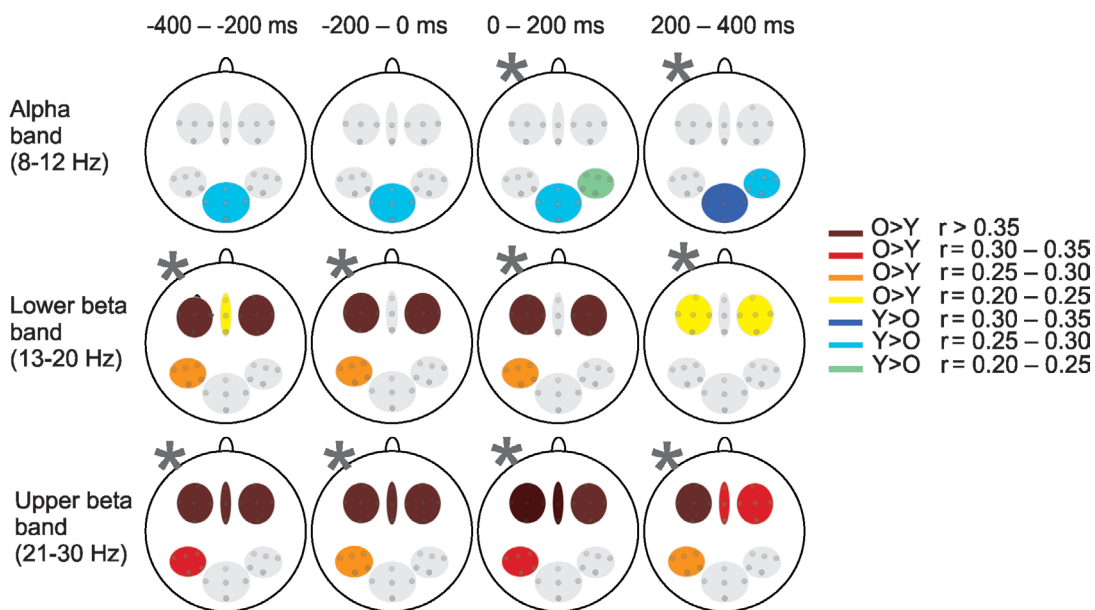


Figure 5.7: **A** Significant correlations ( $r$ ;  $p < 0.05$ ) between power values in different ROIs and

the inhibition inefficiency (pooled over the two age groups). The color of the circle indicates strength and sign of the correlation. **B** Significant differences between age groups ( $p < 0.05$ ) in power values between different ROIs. The color of the circle indicates effect size ( $r$ ) and sign of the difference. An asterisk (\*) indicates that the number of significant correlations or group differences in that time-frequency bin exceeds the number expected by chance ( $p < 0.05$ ).

### 5.5 Discussion

The main aim of the present study was to examine age-related changes in inhibition of irrelevant information, taking into account differences between high and low performing individuals. We used a combination of behavioral, ERP, power and functional connectivity measures to reveal neural correlates of efficient inhibition in younger and older participants. More specifically, we used P1 and N1 ERP component amplitudes to investigate whether inhibition inefficiency was related to insufficient suppression of irrelevant visual information in early processing stages. Phase locking analyses between frontal and occipito-parietal ROIs in the alpha and beta band were used to test whether inhibition inefficiency was related to decreased connectivity between these groups of electrodes. Additionally, we tested whether power in the alpha and beta band in frontal and occipito-parietal ROIs was related to inhibition inefficiency.

The behavioral data demonstrated that although participants were instructed to attend only to the relevant diagonal, both younger and older participants were affected by information presented at irrelevant spatial positions. All participants responded more slowly if an irrelevant target was presented compared to the condition in which only non-targets were presented. Older adults seemed to be more affected by irrelevant information than younger adults as reflected by a larger inhibition inefficiency score. However, this apparent decline with age was carried exclusively by the low performing elderly subgroup. These results clearly indicate that aging does not necessarily lead to a decline in inhibition on a behavioral level; the high performing elderly performed as well as high performing young participants. These results did not change when measures of processing speed were entered as covariates in the analysis, indicating that this is in fact a specific effect of efficient inhibition. The large differences in the decline of inhibitory function between high and low performing elderly underline the importance of looking at individual differences when studying aging.

Mean P1 amplitude in the different groups matched the pattern of results in the inhibition inefficiency scores; old low performers had the most pronounced P1, while young low performers had a larger P1 than young high performers. The P1 reflects the early influence of top-down processes on sensory processing based on global stimulus features (Klimesch et al., 2007; Klimesch, 2011). If a stimulus appears at a spatial location the participant is not attending to, P1 amplitude was found to be smaller than when the same stimulus appears at an attended location (Mangun & Hillyard, 1991). P1 is however not only related to attention to relevant stimuli, but also to suppression of irrelevant

stimuli. In a working memory task, a stimulus elicited a smaller P1 if that stimulus was irrelevant according to the task instructions compared to the same stimulus presented without relevance instruction. This was interpreted as evidence for a reflection of inhibition (Gazzaley et al., 2008). In the current study, we found that participants who were more affected by a target on the irrelevant diagonal had a larger P1. Top-down modulation enables the selection of relevant stimuli and the suppression of irrelevant stimuli through regulation of neuronal excitability (Gazzaley & Nobre, 2012; Kastner & Ungerleider, 2000). In the present study, participants knew before stimulus onset where irrelevant information would appear on the screen. Therefore, they could use this information to apply top-down modulation to the areas processing this information. This could lead to a decrease in the neural excitability of these areas, which in turn could cause the reduction in P1. Therefore, we interpret the increased P1 for low performing participants as reflecting a deficit in inhibition of the information presented at irrelevant diagonals. An alternative explanation might be that the differences in P1 amplitude are related to deficits in lower level visual processing, but since we found no differences in visual acuity between high and low performing participants this explanation seems less likely. We found no differences in P1 amplitude between the various trial types, which is in accordance with the suggestion that P1 reflects early categorization which is based on global stimulus features (Klimesch, 2011) and confirms that the effect we found is indeed related to top-down modulation initiated before stimulus onset. No relation was found between the inhibition inefficiency score and N1 latency or amplitude. The N1 component has been related to the operation of discrimination processes as it is larger in choice reaction time tasks than in simple reaction time tasks, independent of task difficulty (Vogel & Luck, 2000). This shows that inhibition inefficiency is specifically related to inhibition of information at irrelevant spatial locations as reflected in the P1 and not to a general increase in the amplitude of ERP components.

Functional communication between brain areas implicated in the neural network underlying top-down modulation was examined by computing phase locking values in the alpha and beta bands (Sauseng & Klimesch, 2008). We found that specifically in the interval from 400 to 200 ms before stimulus onset, phase locking between frontal and occipito-parietal ROIs in the alpha band was increased for those participants with a lower inhibition inefficiency score, that is, in those who were less distracted by irrelevant target letters. We also found that an increase in alpha power in occipito-parietal ROIs was related to decreased inhibition inefficiency in both younger and older participants. Oscillations in the alpha band have been consistently related to inhibition (Jensen & Mazaheri, 2010; Klimesch et al., 2007). In addition, alpha oscillations are primarily related to top-down communication (Klimesch et al., 2007; Von Stein et al., 2000). In line with these findings, the relation between pre-stimulus phase locking and processing of irrelevant information after stimulus onset might reflect the influence of top-down control via alpha phase locking, modulating cortical excitability in specific cortical areas. Based on task instructions, participants know the position of irrelevant information beforehand;

this information can be used to suppress the excitability of areas processing (ir)relevant stimuli. As the observed increase in phase locking was present in the pre-stimulus interval, an interval during which participants prepared for the upcoming stimulus, it is plausible that the increase in functional communication between frontal and occipito-parietal ROIs indeed represents top down control as opposed to bottom up signaling. Note, however that phase locking is a measure of functional connectivity; therefore it provides no information about the direction of connectivity by itself. Together, these results show that alpha power is indeed associated with increased inhibition and that top down modulation of alpha activity on occipito-parietal electrodes before stimulus onset is associated with efficient inhibition of irrelevant information in both young and elderly.

It has been debated whether increased activity in frontal areas in elderly is beneficial to task performance or is a sign of decline in functional specificity (i.e. dedifferentiation). Some authors claim that patterns of brain activity similar to young participants predict optimal performance (Li & Sikström, 2002; Nagel et al., 2009), while others argue that additional activity in frontal areas contributes to task performance in elderly (Cabeza, 2002; Davis et al., 2008; Reuter-Lorenz & Cappell, 2008). In our data we found differences in power values between older and younger participants which were not related to any of the behavioral measures. Older participants had more power in frontal ROIs than younger participants, mainly in the higher beta band and to a lesser degree also in the lower beta band. In addition the elderly had higher phase locking values between frontal and occipito-parietal ROIs than younger participants across alpha and beta frequency bands, this effect was most clear in the interval from 200 to 400 ms after stimulus onset. On the other hand, we found reduced alpha power in the central occipito-parietal ROI in elderly compared to younger participants over all intervals. Therefore, we hypothesize that the (higher) beta power increases in frontal ROIs and the increase in phase locking, most notably in the intervals after stimulus onset in elderly are used to counteract the decline in alpha power in central occipito-parietal ROIs.

We found that older participants who performed well showed more phase locking between frontal and occipito-parietal ROIs in the higher beta band than low performing elderly over all time intervals. Younger participants showed no correlation between performance and phase locking in this frequency band. Although knowledge about the functional interpretation of beta band oscillations is scarce compared to the alpha band, available evidence links phase locking in the beta band to modulation of attention (Gross et al., 2004; Wróbel et al., 2007; Wróbel, 2000). While phase locking in the alpha band was specifically related to inhibition of the information on irrelevant locations, the higher beta band communication between frontal and occipito-parietal ROIs might be related to the attention attributed to items on the relevant diagonal. It is known that the functional specificity of visual processing areas decreases with age (Park et al., 2004). As a result, increased top-down control of areas processing relevant stimuli might be required for good performance. In addition, the increased phase locking in the beta band might be

used to counteract the effects of reduced alpha power in elderly in the central occipito-parietal ROIs. While the usual approach for detecting compensation mechanisms is to assess activation levels in particular brain areas (Davis et al., 2008; Nagel et al., 2009), our data suggest that it is an increase in communication between areas, specifically in the higher beta band, that is related to effective inhibition in elderly. Considering the specificity of this effect for the elderly group and the strong relation with performance efficiency, we suggest that increased beta band phase locking might represent a neural compensation mechanism employed by high performing elderly. This interpretation is supported by analyses showing that older participants with more phase locking in the upper beta band tended to have a smaller P1 and more pre-stimulus alpha phase locking. Both of these factors were found to indicate a low inhibition inefficiency (good performance) in the current study.

There are several models, which divide attention into subsystems of stimulus selection and conflict resolution. In the current study we focused on the selection of relevant and the exclusion of irrelevant information, which corresponds to the orienting system (Posner & Petersen, 1990; Raz & Buhle, 2006) or the perceptual selection stage (Lavie et al., 2004; Lavie, 2005). Both models suggest that the orienting or perceptual selection stage is automatic and does not require active cognitive control. This assertion is contradicted by a recent study, which has shown that perceptual selection is affected by cognitive load and that distracters can be excluded in the perceptual stage to prevent them from further interference (Caparos & Linnell, 2010). This pattern appears to be reflected in our data as well; the conflict measured with the inhibition inefficiency score between correct letter (response: yes) and incorrect location (response: no) was reduced in high performing participants by employing perceptual selection (as reflected in increased alpha phase locking and decreased P1 amplitude), even before stimulus onset.

In conclusion, we have shown that on a behavioral level, only a subgroup of elderly showed a deficit in inhibition, while others seem to perform comparably to young individuals. This age-related decline in inhibition seems to be related to a deficit in suppression of irrelevant information in the early stages of visual processing, as reflected in the relation between P1 amplitude and the inhibition inefficiency score. Increased top down modulation from frontal to occipito-parietal ROIs in the alpha band and increased alpha power in occipito-parietal ROIs appear to be an underlying mechanisms facilitating performance in both young and elderly participants. The relation between phase locking in the higher beta band and inhibition inefficiency suggests that increases in connectivity in high performing elderly are not passive age related changes but active compensation mechanism employed to maintain adequate performance. Successful ageing seems to be associated with maintenance of efficient information processing capabilities, extended by effective compensation mechanisms resulting in performance levels comparable to young individuals.

# Chapter 6

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The effect of the pre-stimulus brain state on information processing

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Temporal integration depends on increased pre-stimulus beta band power. *Psychophysiology*. 2012



## 6 The effect of the pre-stimulus brain state on information processing

### 6.1 Abstract

Temporal integration was examined using a missing element task, in which task performance depends on the ability to integrate brief successive stimulus displays. Previous studies have suggested that temporal integration is under endogenous control, and that integration is more likely when stimuli match the observer's temporal expectancies. Beta oscillations have previously been related to such cognitive (and attentional) control, as well as to audiovisual integration. We thus hypothesized that pre-stimulus power in the beta frequency band might reflect 'integration readiness', and distinguish trials in which stimuli were successfully integrated from unsuccessful ones. The results showed increased upper beta power (21-30 Hz) prior to successful integration over central and parietal electrodes. This finding supported the idea that increased pre-stimulus beta power might reflect general control processes that can facilitate integration.

### 6.2 Introduction

The ability to perceive events in time allows us to maintain coherency in an ever-changing stream of perceptual input, and enables appropriate actions. Event perception relies heavily on temporal integration: When visual stimuli appear in rapid succession within  $\pm 200$  ms, the brain tends to treat them as a single, integrated event (Eriksen & Collins, 1967). Temporal integration has been observed with various types of stimuli, such as letters that form a word (Forget et al., 2010), two halves of faces (Cheung et al., 2011), and dot matrices (Hogben & Di Lollo, 1974).

Temporal integration is not entirely automatic, however. Several factors influence whether integration will occur. Stimulus characteristics such as duration and luminance affect integration frequency (Di Lollo, 1977; di Lollo, 1980; Hogben & Di Lollo, 1974; Long & Beaton, 1982). Endogenous factors that reflect the state of the observer's cognitive and perceptual system, such as the expected presentation speed (Akyürek et al., 2008), and the availability of (transient) attention, also affect integration (Visser & Enns, 2001; Yeshurun & Levy, 2003). Electrophysiological studies on temporal integration have shown resultant modulations of the N1, N2, P3, and N2pc components of the event related potential (ERP), each of which might indeed relate to endogenous factors (Akyürek et al., 2010; Akyürek & Meijerink, 2012)

However, ERPs do not allow for examination of pre-stimulus effects, which could be important if the state of the perceptual system –even before stimulus onset– indeed



affects temporal integration. Pre-stimulus effects on temporal integration may be detected by examining EEG oscillatory power, in particular in the beta frequency band, which has been related to cognitive control, as well as audiovisual integration (Engel & Fries, 2010; Keil et al., 2012). Both pre- and post-stimulus beta oscillations are also linked to attention (Deiber et al., 2007; Gross et al., 2004; Kranczioch et al., 2007; Wróbel, 2000). A common theme in these studies is that beta power (and/or synchrony) and task performance increase when the perceptual system is optimally set up to process the current or the upcoming stimulus; the latter due to successful prediction, or because the previous stimuli were similar. Importantly, when controlling temporal integration is concerned, this optimal state could be related closely to the currently preferred duration of event timing.

To determine whether pre-stimulus differences in oscillatory power might affect temporal integration, data presented in Akyürek et al. (Akyurek et al., 2010) were presently reanalyzed. In this experiment, participants performed a missing element task (MET), in which two successive stimulus displays (S1 and S2) were presented with a 10 ms interstimulus interval (ISI). Each display contained 12 out of 25 possible squares in a 5x5 matrix. One matrix position remained empty and participants were instructed to localize that missing element. When the two displays are perceived separately, this is very hard to accomplish in a limited amount of time (here 1800 ms). However, when the two displays are temporally integrated into one percept the missing element is easy to spot. When S1 was presented for 70 ms and S2 for 10 ms, participants responded correctly in about half of the trials. This allowed a comparison of the trials in which temporal integration occurred with trials in which it did not. Based on the literature described above, we expected increased pre-stimulus beta power on trials in which temporal integration eventually succeeded.

## 6.3 Methods

### 6.3.1 Participants

Twenty-one students (18 female, 3 male) with normal or corrected-to-normal vision and a mean age of 23 years (range 19-30 years) participated in the study. This study presents a new analysis of the EEG data collected in Experiment 4 of Akyürek, Schubö & Hommel (2010). Further details with regard to its design and execution are reported there.

### 6.3.2 Stimuli and task

Participants searched for the missing element in a MET, consisting of two successive display frames, each containing a random selection of 12 out of 25 possible squares (without overlap), so that only one square was not drawn in either display. In the condition exclusively analyzed here, S1 was presented for 70 ms, followed by a 10 ms blank, and followed by S2 for another 10 ms. Participants responded to a prompt showing all matrix positions, which appeared 600 ms after stimulus offset, and which remained onscreen until a response was registered or 1200 ms had elapsed. After a blank screen with a (random) duration of 600-800 ms, the next trial started.

### 6.3.3 Electrophysiological recording and data analysis

EEG was recorded with 64 Ag-AgCl electrodes laid out according to the extended international 10–20 system. The electrodes were referenced to Cz and re-referenced off-line to the average of both mastoids. Horizontal and vertical eye movements were recorded from the outer canthi of the eyes and above and below the left eye, respectively. Electrode impedance was kept below 5 k $\Omega$ . Data were recorded with a 500 Hz sample rate, and a 125 Hz-lowpass and a 0.1-Hz highpass filter. Off-line, the data were filtered with a 100-Hz lowpass filter and a 0.16-Hz highpass filter (both 48 dB/oct). Subsequently, the data was segmented into 2500 ms segments, starting 1000 ms prior to the onset of S1 and ending 1500 ms afterward. Ocular artifacts (blinks and eye movements) were corrected using the Gratton–Coles procedure (Gratton et al., 1983). Trials with voltage steps exceeding 50 mV/ms were excluded from analysis.

The analysis compared trials with unsuccessful temporal integration to trials with successful integration, as evidenced by the participants' response accuracy (excluding missing responses). Time–frequency analyses were performed with the Matlab-based FieldTrip toolbox (Oostenveld et al., 2011) using Morlet wavelets. This analysis produced an estimate of oscillatory raw power for each time sample between 600 ms pre-stimulus and 600 ms post-stimulus (in 10 ms steps) and for each frequency between 8 and 60 Hz (in 0.5 Hz steps). The Morlet wavelets contained a fixed number of cycles of sinusoidal oscillations for each frequency band (8-12 Hz, 6 cycles; 13-20Hz, 7 cycles; 21-30 Hz, 8 cycles; 31-60 Hz, 9 cycles). Subsequently, following Grandchamp and Delorme (2011), a relative baseline correction was applied in which the power on each time point and frequency was divided by the average power of that frequency in the entire epoch (-600 ms to 600 ms) for each channel separately. This procedure reduces the effect of artifactual trials with high power estimates.

A non-parametric cluster based randomization technique was used to identify whether the power was different for correct and incorrect trials (Maris & Oostenveld, 2007). This method deals with the multiple comparisons problem, while accounting for the dependency of the data, by clustering neighboring samples that show the same effect.

The analysis was performed separately for the average power in each of four frequency bands, alpha (8-12 Hz), lower beta (13-20 Hz), upper beta (21-30 Hz) and gamma (31-60 Hz). Independent samples t-tests (correct vs. incorrect trials) were performed on all channels and time points. Samples in which this t-value exceeded an uncorrected threshold of  $p < 0.05$  were subsequently clustered. The sum of the t-values within a cluster was used as the cluster-level statistic. By randomizing the data across the two conditions and recalculating the test statistic 2000 times, a reference distribution of maximum cluster t-values was generated to evaluate the statistic of the actual data.

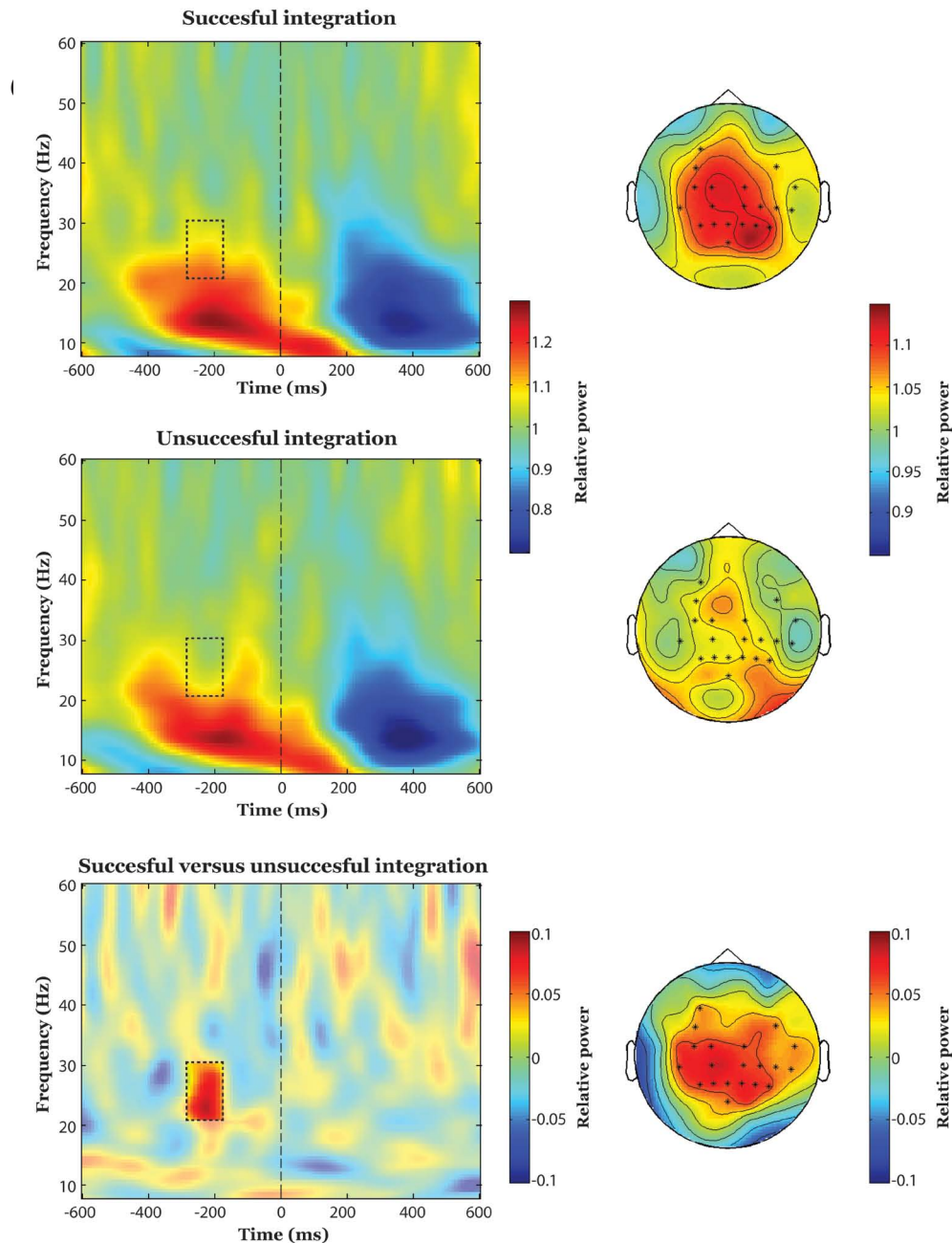


Figure 6.1: Time-frequency plots for successful integration trials, unsuccessful integration trials and the difference between successful and unsuccessful integration trials. The plots show

relative power (dB) averaged over the 5 electrodes showing the strongest differences between these conditions (P1,P2,P3,CP1,CP3). The dashed square indicates where successful and unsuccessful integration trials were significantly different. The scalp maps represent relative power distributions (calculated over the upper beta average) over the scalp at 230 ms before stimulus onset. The stars indicate electrodes that belong to the cluster that shows a significant difference between the trial types.

As reported previously by Akyürek et al. (2010), temporal integration was achieved in approximately half the trials (mean correct = 52.1%, SEM = 3.1%). The cluster-based randomization technique revealed that power in the upper beta band (21-30 Hz) between 280 and 180 ms before stimulus onset (see figure 6.1) was significantly higher in successful integration than in unsuccessful integration trials ( $p=0.02$ ). Tests in the alpha ( $p=0.94$ ), lower beta ( $p=1$ ) and gamma bands ( $p=0.57$ ) did not show significant results, either pre- or post-stimulus. The upper beta effect was mainly present over parietal and central electrodes.

### 6.5 Discussion

Consistent with our expectations, pre-stimulus oscillatory power was related to temporal integration. Specifically, pre-stimulus upper beta power (21-30 Hz) over parietal and central electrodes was significantly higher in trials with stimulus integration compared to trials without. Together with previous evidence that temporal integration is under endogenous control, the present findings are compatible with one hypothesized role of beta band oscillations in the maintenance of the status quo of the perceptual system (Akyürek et al., 2008; Engel & Fries, 2010). The data thus suggested that integration is most likely to succeed when the perceptual system is optimally tuned for the upcoming task, which likely requires adopting a relatively long integration window, able to encompass the two successive stimuli. This may be one way in which beta activity is related to temporal (onset) expectations (Cravo et al., 2011), which may eventually also subserve motor planning (Alegre et al., 2003).

Such optimization of the state of the perceptual system may be related to the availability of attention. Indeed the current results provide support for the idea that attention facilitates temporal integration (Visser & Enns, 2001; Yeshurun & Levy, 2003). Several studies have related beta synchrony and beta power to attention. Increased beta power has been related to higher performance in vigilance tasks (Belyavin & Wright, 1987), and was found to increase during stimulus expectancy periods (Basile et al., 2007). Beta synchrony has furthermore been found to predict the perception of briefly presented visual stimuli (Hanslmayr et al., 2007), the perception of the second target in attentional blink tasks (Gross et al., 2004; Kranczioch et al., 2007), and the application of top-down attentional control (Buschman & Miller, 2007). The present increase in beta power before stimulus onset fits well with the idea that (anticipatory) attention may facilitate temporal integration. Behaviorally, this may also transpire in longer perceived durations of attended

stimuli (e.g., Enns et al., 1999). Whether these effects reflect spontaneous waxing and waning of attention over trials, or active preparation for upcoming stimuli remains to be determined.

The perceptual state reflected by the pre-stimulus beta activity cannot only reflect an increased ability to discern stimuli; in the present task this could lead to the arguably more accurate perception of two successive stimuli, rather than one integrated percept. Thus, the present beta activity must also reflect an increased tendency to integrate sensory input. In one previous study increased pre-stimulus beta power has been related to auditory-visual integration (Keil et al., 2012), in which beamformer source analysis pointed to a network of left superior temporal gyrus, precuneus and right middle frontal gyrus. In another study by Hipp, Engel and Siegel (2011) beta band synchronization in a similar fronto-parietal-occipital network also predicted integration of visual and auditory information. The current results may be related to these findings by assuming that pre-stimulus beta power might reflect processes that facilitate integration in general; both between modalities as well as in the temporal domain.



# Chapter 7

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An fMRI study on the neural correlates of selective attention in old and young

Submitted as:

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Brain mechanisms underlying the effects of aging on different aspects of selective attention.



## 7 An fMRI study on the neural correlates of selective attention in old and young

### 7.1 Abstract

The ability to suppress irrelevant information declines with age, while the ability to enhance relevant information remains largely intact. We examined mechanisms behind this dissociation in an fMRI study, using a selective attention task in which relevant and irrelevant information appeared simultaneously. Slowing of response times due to distraction by irrelevant targets was larger in older than younger participants. Increased distraction was related to larger increases in activity and connectivity in areas of the dorsal attention network, indicating a more pronounced (re-)orientation of attention. The decreases in accuracy in target compared to nontarget trials were smaller in older compared to younger participants. In older adults we found increased recruitment of areas in the fronto-parietal control network (FPCN) during target detection. Moreover, older adults showed increased connectivity between the FPCN, supporting cognitive control, and somatomotor areas implicated in response selection and execution. This connectivity increase was related to improved target detection, suggesting that older adults engage additional cognitive control, which might enable the observed intact performance in detecting and responding to target stimuli.

### 7.2 Introduction

Every second, the human retina can send around 10 million bits of information to the brain (Koch et al., 2006). With such enormous quantities of information, the selection of behaviorally relevant pieces of information is essential. Two separate top-down modulatory mechanisms have been suggested to underlie selection of relevant information; suppression of irrelevant information and enhancement of relevant information (Gazzaley et al., 2005a; Hillyard et al., 1998).

Aging affects selective attention. Previous research has shown that task performance in older adults is especially affected by the presence of irrelevant stimuli compared to younger adults (de Fockert et al., 2009; Haring et al., 2013; Mager et al., 2007; Schmitz et al., 2010). This is reflected in increased slowing of response times when participants are presented with distracting stimuli (Geerligs et al., 2012b). Using a working memory paradigm, in which to be remembered and to be forgotten information was presented sequentially, the Gazzaley group showed that older adults indeed had trouble suppressing irrelevant information, whereas enhancement of relevant information was found to be intact (e.g. Gazzaley et al., 2005a; Gazzaley et al., 2008; for a review see Gazzaley, 2011). Moreover, they found that the decreased ability to suppress irrelevant information was

related to decreased memory capacity for relevant information (Gazzaley et al., 2008).

It should be noted that not all studies have found a deficit in the suppression of irrelevant information with age (e.g. Kramer et al., 1994; Wild-Wall et al., 2008). It has been suggested that enhancement of relevant stimuli might actually be amplified in older compared to younger participants to overcome the age-related deficits in suppression (Haring et al., 2013; Wild-Wall et al., 2008). However, it has also been shown that under higher levels of visual load, that is in the context of distracting information, older adults do have trouble enhancing relevant stimuli (Chee et al., 2006). Quigley and colleagues (2010), for example, instructed participants to detect the direction of motion in a cloud of dots, all in one color. In addition, they superimposed another cloud of dots in a different color that acted as distractors. A cue indicated which color participants should attend to. Using an EEG technique (frequency tagging), the authors showed that younger adults clearly enhanced processing of stimuli with a relevant color. Older adults, however, showed no enhancement of relevant stimuli with respect to the pre-cue period and were significantly less accurate than young adults in detecting coherent motion. This suggests that when relevant and irrelevant information is present simultaneously, older adults can have trouble enhancing relevant information. It has been shown that declines in the visual system can cause deficits in the detection of briefly presented stimuli (e.g. Eriksen et al., 1970). However, as the stimuli in the Quigley et al. (2010) study were presented for a long period of time (2.2 seconds), this is unlikely to be the cause of the deficit in enhancement.

Top-down modulation of visual stimulus processing relies on a network of frontal and parietal brain regions, the dorsal attention network (DAN), operating in close interaction with the sensory cortices (Corbetta & Shulman, 2002; Desimone & Duncan, 1995; Kastner & Ungerleider, 2000). The main components of this DAN are the frontal eye fields (FEF) and the superior parietal lobule (SPL). Signals from these areas cause changes in the baseline firing rates of neurons and neural synchronization, leading to a larger neural responsiveness in the sensory cortices when a stimulus is attended (Reynolds & Chelazzi, 2004). This increased neural responsiveness is visible in the increased amplitude of early event related potentials (ERPs) and increased blood oxygen level-dependent (BOLD) signals for attended stimuli (Gazzaley et al., 2005a; Hillyard et al., 1998) and leads to an increased ability to detect stimuli with attended spatial or non-spatial features. For unattended stimuli the opposite pattern emerges; neural responsiveness is reduced leading to decreased stimulus detection.

The mechanism described above allows segregation of relevant from irrelevant information in perceptual stages of processing. This requires that previous knowledge on the features or locations of relevant information and the task goals is maintained in working memory, involving activation of the fronto-parietal control network (FPCN). This network consists of the dorsolateral prefrontal cortex (DLPFC), the inferior and superior

parietal cortex, the rostralateral prefrontal cortex (RLPFC) and the cerebellum. The FPCN has been found to be active in a wide range of tasks involving cognitive control (for a meta-analysis see: Niendam et al., 2012) and has especially been linked to goal-directed cognition (Braver et al., 2009; Spreng et al., 2013; Spreng et al., 2010a; Vincent et al., 2008).

It has been suggested that older adults increasingly rely on the resolution of interference in later stages of processing (reactive control), to mitigate the effects of a reduced ability to prevent interference (proactive control, Braver et al., 2007; Braver, 2012). This is in line with a number of studies that have shown that (part of) the age-related impairment in selective attention stems from changes in perceptual stages of processing (de Fockert et al., 2009; Haring et al., 2013; Schmitz et al., 2010), which are likely to be related to reduced preparation for the upcoming stimulus (Geerligs et al., 2012b). However, so far it is not clear whether older adults can actually use additional reactive control mechanism in selective attention tasks to mitigate the effect of aging on proactive control. In the current study, we investigated whether there is evidence for increased use of reactive control mechanisms in older adults by increased recruitment of areas involved in the resolution of conflict, such as the FPCN or the anterior cingulate cortex (Carter & Van Veen, 2007).

Many studies examining the effects of aging on selective attention have either separated the relevant and irrelevant information in time, or spatially superimposed the relevant and irrelevant stimuli (e.g. de Fockert et al., 2009; Gazzaley et al., 2005a; Gazzaley et al., 2008; Quigley et al., 2010). This is unlike situations often occurring in daily life, in which relevant and irrelevant information are typically spatially segregated. In the current study, we therefore use a selective attention task in which relevant and irrelevant information is presented simultaneously at different spatial locations. Participants are informed about the relevance of a location (i.e. one of the diagonals of a square) and about the letter identity of the "target" stimulus before each task block. The instruction is to identify a target stimulus among other stimuli, but only if it appears on a relevant location. This compares well to, for example, the real world situation of detecting a green light appearing in traffic lights. If the green light appears at another location, the 'target' needs to be ignored and is considered irrelevant.

In the selective attention task used here, participants responded by pressing a predefined button when the target appeared on a relevant spatial location. An alternative button was pressed if the target did not appear or if the target appeared on an irrelevant spatial location. Using the nontarget condition as a baseline, we were particularly interested in the effect of a target stimulus (detection effect) and the effect of an irrelevant target; that is, a target at an irrelevant spatial location (distraction cost), on response times, accuracy and neural measures. All three task conditions require adequate enhancement of relevant information as well as suppression of irrelevant information. However, by examining the change in response time between nontargets (i.e. no target letter presented) and irrelevant targets (i.e. target letter presented at an irrelevant diagonal position), we can infer to what

extent the participant is able to suppress information presented on the irrelevant diagonal. If the participant is distracted by the irrelevant target, we would expect responses to be slower for irrelevant targets compared to nontargets. In the same way, comparing the nontarget condition to the target condition will provide information about how well participants are able to enhancing the processing of relevant stimulus features as well as relevant spatial locations. Using these different task conditions therefore, allowed us to study the effects of aging on reactive control during enhancement and suppression.

Based on the literature described above, as well as the results from our previous study using a highly similar task (Geerligs et al., 2012b), we expect that older adults will show increased distraction costs, particularly in response times. In the current study, we investigate the differences between age groups on reactive control mechanisms in selective attention, by comparing the neural signatures of the different task conditions. Early selection processes, that arise as a result of differences in proactive control, are expected to be the same over the different task conditions that contain highly similar visual stimuli. However, if older adults are able to use reactive control mechanisms to support selective attention, we would expect to find additional activation in brain areas involved in the resolution of conflict, such as the FPCN or the anterior cingulate cortex (Carter & Van Veen, 2007). This additional activation would be expected to be related to higher levels of performance in older adults. If no difference is detected in activation of these brain areas between age groups, this would suggest that older adults do not use more reactive control processes than young participants. Because selective attention requires the collaboration of different sets of brain regions, we investigated task dependent modulations in both activity and functional connectivity.

## 7.3 Materials and methods

### 7.3.1 Participants

Forty younger (21 males,  $M_{\text{age}} = 20.6$  years, age range: 18-26 years) and 40 older adults (24 males,  $M_{\text{age}} = 64.9$  years, age range: 59-74 years) participated in the experiment. All participants were right handed and did not have a history of neurological or psychiatric disorders. They had normal or corrected-to-normal visual acuity. The older participants scored 26 or higher on the Mini Mental State Examination (MMSE, Folstein et al., 1975) and below 16 on both subscales of the Hospital Anxiety and Depression Scale (HADS, Zigmond & Snaith, 1983). Twelve older participants took medication against high blood pressure, high cholesterol or heart failure. Ten of those participants were included in the final sample (see below for reasons for exclusion). From one older participant, data on medication use was not available. Levels of education were similar in both age groups, with an average number of 16.09 years of education in the young participants and 16.34

years in the older participants. The study adhered to the Declaration of Helsinki and was approved by the local ethics committee of the University Medical Center Groningen, the Netherlands. Informed consent was obtained from all participants. Data of one older participant was lost due to technical problems. One older participant was excluded because a brain abnormality was detected.

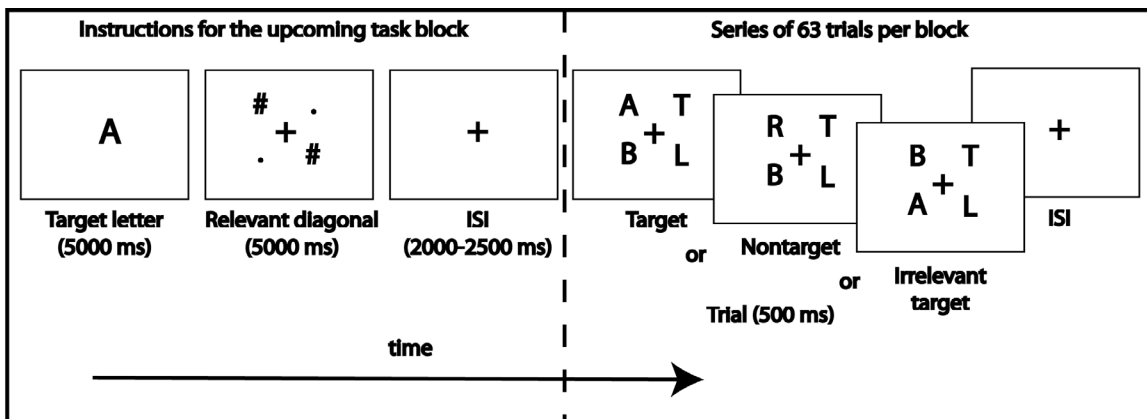


Figure 7.1: A schematic overview of the selective attention task

### 7.3.2 Stimuli and Apparatus

Stimulus generation and response collection were controlled using E-prime 1.2 (Psychology Software Tools, Inc., Sharpsburgh, PA). Figure 7.1 depicts a schematic illustration of the selective attention task that was used. At the start of each experimental block, participants were presented with a single target letter (5000 ms), followed by a frame which indicated on which display positions (right-up or left-up diagonal positions) relevant information could be presented for that block. After instructions, 6 blocks, each containing 63 trials were presented. The target letter, as well as the relevant diagonal, was different in different blocks. Blocks were followed by a 30 second fixation cross. In each trial, the stimuli, consisting of 4 letters arranged in a square, were presented for 300 ms followed by an interstimulus interval varying randomly between 2000 and 2500 msec. A fixation cross in the middle of the screen remained visible throughout a block of trials. Participants were instructed to press the ‘yes’ button when the target letter was presented on a relevant diagonal position [target T]. When a target letter appeared on one of the irrelevant diagonal positions [irrelevant target IT] or when no target letter appeared at all [nontarget NT], participants were required to press no. Right hand index and middle finger responses were given for ‘yes’ and ‘no’ responses, randomized over participants. Relevant target trials made up 33% of the total number of trials, therefore 33% of trials required a ‘yes’ response whereas 66% of trials (irrelevant targets and nontargets) required a ‘no’ response. There were never two target letters present in one stimulus frame. All stimuli were white letters in Arial font, size 18, presented on a black screen. Stimulus letters were randomly chosen from the alphabet, excluding the letters g, i, o, q, u, x, and

y. All participants practiced the task on two occasions. In the week before the scanning session participants came in for the screening and practiced the task for 2 blocks of 40 trials. Right before the scanning session they practiced the task again until it was clear that they understood the instructions.

### 7.3.3 Behavioral data

Data of three younger participants and one older participant were excluded from the analyses because their accuracy was around chance level (below 60%) in one or more task conditions. Fast guesses (responses faster than 200 ms) and responses slower than the minimum interstimulus interval (2000 ms) were regarded as incorrect responses. The behavioral data was analyzed using a repeated measures analysis in SPSS (version 20.0), using the within subjects factor task condition and the between subjects factor age group. P-values were adjusted for violations of the sphericity assumption using the Greenhouse-Geisser correction (Greenhouse & Geisser, 1959). For clarity, uncorrected degrees of freedom values are presented in the results section. Paired and independent samples t-tests were used for post-hoc testing.

There were two outcome measures of interest in this task. First, selective attention to relevant target stimuli as measured by the difference in response time (RT) and accuracy (ACC) between target (T) and nontarget (NT) trials ( $RT_{T-NT}$  and  $ACC_{NT-T}$ ). Although different processes might underlie the differences in response time and accuracy between T and NT trials, we refer to this difference as detection effect. Second, distraction by irrelevant information, was measured by the difference in RT between irrelevant target trials (IT) and NT trials ( $RT_{IT-NT}$ ). When attention is drawn to the irrelevant target letter, attention needs to be re-oriented, which is associated with an increase in response times; this will be referred to as distraction cost. The accuracy scores were not taken into account for the IT-NT contrast, as 31 of the 65 (19 older and 12 younger) participants included in the final sample (see below) showed a decline in accuracy smaller than 1%, indicating a ceiling effect for these participants. To compute the relation between performance and BOLD activity and connectivity values, scores were z-transformed for older and younger participants separately, resulting in a performance measure that is corrected for age group. This was done to ensure that there was no overlap in the variance that can be explained by the effect of performance and the effect of age group.

### 7.3.4 Image acquisition

fMRI scans were obtained with a three tesla MR scanner (3T Achieva, Philips Medical Systems, Best, Netherlands), with echo planar imaging (EPI) capability and an eight channel SENSE head coil during performance of the selective attention task, as well as



during 10 minutes of eyes closed resting state. Functional images were obtained with the following pulse sequence parameter settings: single shot EPI; 37 slices; slice thickness 3.5 mm; no gap; field of view 224 mm; matrix scan size 64 by 64; transverse slice orientation; repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; minimal temporal slice timing (1836 ms); flip angle 70°. The first three scans of each run were discarded to avoid spin-history artifacts. A 3-D T1-weighted anatomical scan of the entire brain was obtained for each participant using the following pulse sequence parameters: field of view 256 mm; matrix scan size 256 by 256; 170 slices; slice thickness 1 mm; transverse slice orientation; TE = 3.6 ms; TR = 9 ms; flip angle 8°.

### 7.3.5 fMRI data analysis

Offline processing was performed using the statistical parametric mapping software package (SPM 8; <http://www.fil.ion.ucl.ac.uk/spm/software>). The functional images were motion-corrected and coregistered to the anatomical scan. The coregistration was checked visually and adjusted manually when required. Bias regularization (SPM 8) was used to reduce signal intensity variations due to field inhomogeneities in both structural and functional images. For functional images, the regularization was initially applied to the first and the last functional scan. Based on these two corrections, an average correction factor was computed for each voxel, which was applied to all scans. A group specific anatomic template was created (for young and older participants together), using Diffeomorphic Anatomical Registration Exponentiated Lie algebra (DARTEL), to optimize inter-participant alignment (Ashburner, 2007). Data were smoothed with an 8 mm full-width half maximum (FWHM) Gaussian kernel.

T, NT and IT trials were modeled as separate regressors. Other regressors included the motion parameters and the first derivatives of the motion parameters. In addition, to take the low frequency cycling of task blocks into account, a high pass filter of 230 seconds was used. After realignment and inclusion of motion parameters in the design, participant motion can still influence beta values and connectivity estimates (Power et al., 2012). Therefore, an additional procedure was applied to restrict the influences of movement on functional connectivity. Initially, scans which were affected by motion were identified in two steps. First, single scans with a total displacement of more than 0.5 mm with respect to the previous scan were identified. Second, single scans with a root mean squared intensity change (with respect to the previous scan) of more than 3 standard deviations were identified. To make sure these scans did not affect functional connectivity, the identified scans, as well as one scan before and two scans after the identified scans, were flagged and modeled as separate regressors (flagged scan regressors). For each flagged scan, a regressor was made that contains a "1" for the flagged scan and zeros for all other scans. In addition to the participants excluded based on behavioral data, seven younger and two older participants were excluded from the analysis because of



excessive movement during the fMRI scan (more than 140 scans deleted after the motion correction procedure). All of these excluded participants moved more than 3 mm over the course of the scan and moved more than 0.5 mm in more than a total of 35 scans. The final sample consisted of 30 younger and 35 older participants.

Similar to Geerligs et al. (2012a), we used the canonical hemodynamic response function (HRF), as well as, the derivative and the dispersed to model the effects of task condition. We combined these three estimates by calculating the area under the curve (AUC, Geerligs et al., 2012a). AUC values were divided by the beta of the constant term of the model per voxel to correct for initial offset differences. To facilitate the reporting of the AUC values, they were subsequently multiplied by 1000. The resulting values were used in a factorial analysis of variance on second level, including the factors task condition and age group. A FWE cluster correction of 0.05 (initial threshold  $p < 0.001$ ) was used to identify areas showing a main effect of task condition or an interaction between age group and task condition. ROIs were defined based on these results, as the peak activations surrounded by a 10 mm diameter sphere. To additionally assess the relation between performance and BOLD activation in both age groups, mean AUC values for the T-NT contrast and the IT-NT contrast were extracted from each of these ROIs.

### 7.3.6 Functional connectivity analyses

Prior to the functional connectivity analysis we applied a slightly different approach to remove variance in the data related to noise, such as participant motion, and cardiac and respiratory cycle (Van Dijk et al., 2010). In addition, variance associated with task execution was removed from the data. A general linear model (GLM) approach was used, which included all regressors in the first level design (task as well as nuisance regressors), except the flagged scan regressors, which were used in a subsequent analysis step. In addition, time-courses from the white matter, cerebro-spinal fluid and the whole brain and first derivatives of these signals were included in the GLM (for details of this procedure see Geerligs et al., 2012a). The residual images obtained after this approach contained only the variance that could not be explained by these regressors. For each of the previously defined ROIs, the first eigenvariate of the time course was extracted from the residual images.

To investigate the effects of task condition on functional connectivity, we developed a procedure which relies on correlations instead of regression analysis, which is used in the traditional psychophysiological interaction (PPI) analysis (Friston et al., 1997). Theoretically, it is clear that the functional connectivity from region "A" to region "B" should be the same as the functional connectivity from "B" to "A". However regression analysis in PPI analysis can give different results depending on the chosen seed region (A or B). The current approach circumvents this problem by using correlation analyses

instead. Another advantage of the current approach is that correlations are computed on the deconvolved signal, which is expected to reduce the influence of temporal variations in BOLD response.

ROI time courses were first deconvolved using the algorithms implemented for psychophysiological interaction analysis in SPM8 (Gitelman et al., 2003). The flagged scans, indicating scans affected by participant motion, were still included in the deconvolved time courses. Therefore, we performed an intermediate correction step. First, the flagged scan regressors were deconvolved, using the same algorithm as applied for the time course data. This produces a time course similar to what would be expected when a sudden intensity change due to abrupt movement was deconvolved. Subsequently, the deconvolved flagged scan regressors were used in a regression analysis to predict the deconvolved time course of each ROI. The residuals of this regression analysis were maintained and used for subsequent analyses. The next step in the analysis, was to convert the stimulus onsets to the same time base as the deconvolved scans (microtime in SPM) in order to produce three vectors of onset times, one for each task condition. Correlations between all the deconvolved ROI time courses were computed for each of the task conditions separately, by selecting only those time points on which a stimulus belonging to that task condition was presented. In addition, the average correlation between all ROI time courses over all task conditions was computed.

Resting state data was processed in the same way as the task data, except for the removal of variance associated with task execution. Data of two participants from the final sample of 65 participants were not taken into account in the analysis of the resting state data as more than 100 of the total number of 300 scans were removed due to the motion correction procedure in these individuals. All time points in the resting state data were used to compute the correlations between ROI time courses. There has been considerable debate about the use of global signal regression in resting state data. The global signal reflects a combination of resting-state fluctuations, physiological noise (e.g. respiratory and cardiac noise), and other noise signals (Birn et al., 2006). With advancing age, the (physiological) noise in the BOLD signal increases (D'Esposito et al., 1999; Makedonov et al., 2013) and global signal regression might reduce the effects of these noise differences between age-groups on functional connectivity estimates. However, other researchers have claimed that application of global signal regression can bias the results of group comparisons (Saad et al., 2012). Therefore we have performed the resting state analysis both with and without global signal regression.

### 7.3.7 Linear mixed effects models

For the analysis of the ROI BOLD data and the ROI connectivity data, maximum likelihood based linear mixed effects models were used. To this end, the `lmer` function

implemented in the lme4 package (Bates et al., 2012) in R (R Core Team, 2012) was used. To estimate the p-values for each of the factors in the model, we used the package lmerTest, which uses the Satterthwaite approximation for the denominator degrees of freedom or the F-statistic (Kuznetsova et al., 2013). For clarity, the reported degrees of freedom were rounded to the nearest integer value. In all analyses, age group was included as a fixed factor using effect coding; the effect coding was adjusted for the number of participants in each group so that the average value for this factor over all participants was zero. For all fixed factors included in each of the models, we investigated the main effects as well as the interactions between the different fixed factors.

## 7.4 Results

### 7.4.1 Behavioral data

In general, older participants had longer response times ( $M=685$ ,  $SD=84$ ) than younger participants ( $M=523$ ,  $SD=70$ ;  $F(1,68)=81.80$ ,  $p<0.001$ ). However, these effect of age group were modulated by task condition (task:  $F(2,126)=57.89$ ,  $p<0.001$ ; task\*age group:  $F(2,126)=27.02$ ,  $p<0.001$ ). All participants responded faster to nontarget (NT) than to irrelevant target trials, although, this effect was larger for older than younger participants (age\*IT-NT:  $F(1,63)=18.02$ ,  $p<0.001$ ; young:  $t(29)=8.01$ ,  $p<0.001$ ; old:  $t(34)=8.89$ ,  $p<0.001$ ). Responses to target (T) trials were also faster than responses to IT trials, but only for older and not for younger participants (age\*T-IT:  $F(1,63)=39.03$ ,  $p<0.001$ ; young:  $t(29)=1.47$ ,  $p=0.15$ ; old:  $t(34)=8.87$ ,  $p<0.001$ ). Young adults responded slower to T than NT trials, whereas, this effect was reversed in older participants (age\*T-NT:  $F(1,63)=15.63$ ,  $p<0.001$ ; young:  $t(29)=3.37$ ,  $p=0.002$ ; old:  $t(34)=2.50$ ,  $p=0.018$ ).

Overall, accuracy levels were similar for older and younger participants ( $F(1,63)=1.39$ ,  $p=0.24$ ), but accuracy levels were modulated by task condition (task:  $F(2,126)=58.31$ ,  $p<0.001$ ; age\*task  $F(2,126)=3.22$ ,  $p=0.054$ ). Participants generally made more errors in IT than NT trials (young:  $t(29)=4.48$ ,  $p<0.001$ ; old:  $t(34)=2.08$ ,  $p=0.045$ ) and this was similar in both age groups (age\*IT-NT :  $F(1,63)=0.53$ ,  $p=0.47$ ). Participants also made more errors in IT trials than T trials and this effect was stronger in younger than older participants (age\*T-IT:  $F(1,63)=4.35$ ,  $p=0.041$ ; young:  $t(29)=6.16$ ,  $p<0.001$ ; old:  $t(34)=5.06$ ,  $p<0.001$ ). In addition, performance on T trials was less accurate than on NT trials, but this effect was larger in younger than older participants (age\*T-NT:  $F(1,63)=4.07$ ,  $p=0.048$ ; young:  $t(29)=7.44$ ,  $p<0.001$ ; old:  $t(34)=4.91$ ,  $p<0.001$ ). Means and standard deviations of response times and accuracy scores can be found in table 7.1.

To ensure that the response time differences between conditions were not the result of general slowing phenomena in the older group (Salthouse, 1996), we repeated the

analysis in which the difference scores  $RT_{T-NT}$  and  $RT_{IT-NT}$  were divided by the average response time in the NT trials. T-tests confirmed that the effects were not due to age-related to slowing, as the effects of aging on the proportional difference score were similar to the effects of aging on the original response time data ( $RT_{T-NT}$ : young=0.037, old=-0.022,  $t(60.7)=4.4$ ,  $p<0.001$ ;  $RT_{IT-NT}$ : young=0.053, old=0.089,  $t(58.5)=3.2$ ,  $p=0.002$ ).

Table 7.1: Mean (standard deviation) response times and accuracy scores for each task condition and age group.

	Nontarget	Target	Irrelevant Target
RT Young	509 (72)	526 (71)	534 (74)
RT Old	670 (86)	654 (74)	730 (101)
ACC Young	98.4 (0.2)	89.2 (0.7)	95.4 (0.4)
ACC Old	98.1 (0.3)	92.4 (0.7)	96.1 (0.6)

#### 7.4.2 Irrelevant targets versus nontargets

Large parts of the dorsal attention network (DAN) were more active in IT compared to NT trials. This activity increase was found in the right hemisphere, in the inferior and superior parietal and middle occipital gyri, as well as the frontal eye fields (FEF), the inferior frontal operculum and the inferior temporal gyrus (figure 7.2 and table 7.2). In the left hemisphere, activity was increased in the middle occipital and inferior and superior parietal gyri as well as in the cerebellum. No significant differences were observed between the two age groups.

Table 7.2: Areas in which BOLD activation increased significantly ( $P_{FWE}<0.05$ ) in irrelevant target, compared to nontarget trials.

Irrelevant targets > Nontargets	k	T	x, y, z (MNI)
R Mid Occipital (BA 19)*	14409	8.48	32 -72 34
R Sup Parietal (BA 7) *		8.13	18 -66 58
L Mid Occipital (BA 19)		7.25	-28 -74 28
L Sup Parietal (BA 7)*		6.77	-16 -64 60
L Inf Parietal (BA 40)*		5.57	-40 -42 48
L Cerebellum 6		5.33	-28 -66 -28
R Frontal Eye Fields (BA 8)	733	6.66	22 6 52
R Inf Frontal Operculum (BA 44/48)	514	4.34	40 16 28
L Frontal Eye Fields (BA 6)*	409	4.25	-28 0 58

L=left, R=right, BA=Brodmann's area, x,y,z=stereotactic coordinates, k=cluster extent, Mid=middle, Inf=inferior, Sup=superior. \* indicates areas in which the activation increase (IT>NT) was related to increased distraction cost ( $RT_{IT-NT}$ )

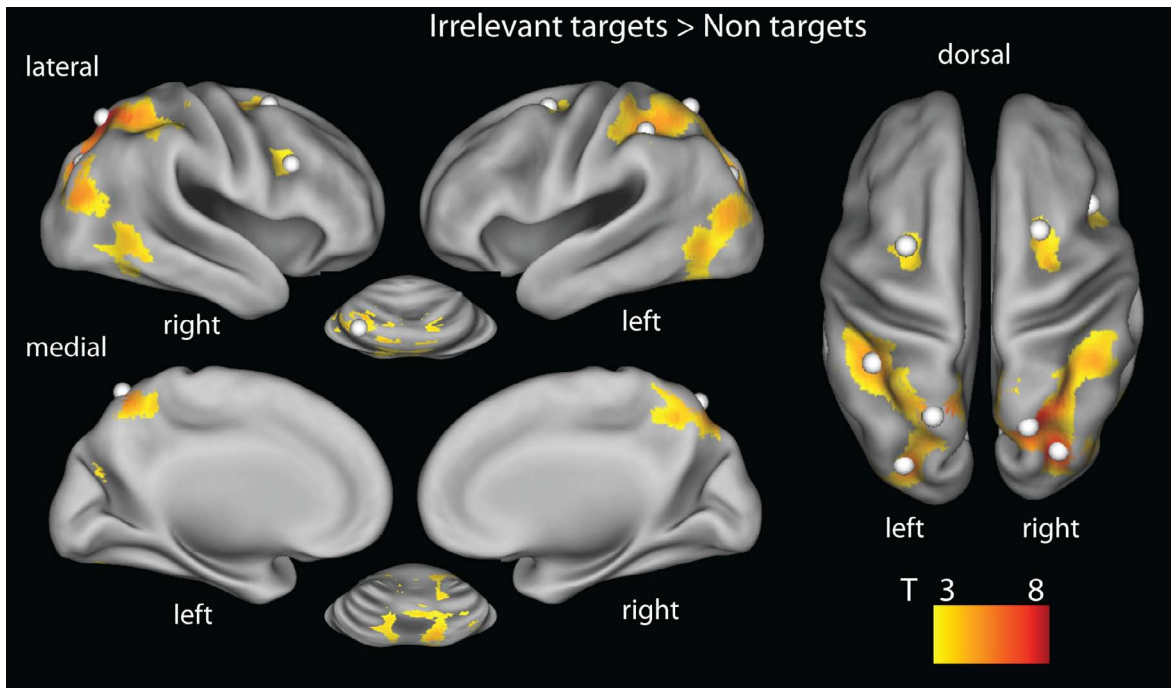


Figure 7.2: Areas which were more active in irrelevant target compared to nontarget trials ( $P_{FWE} < 0.05$ ). The white spheres indicate the centers of the associated ROIs, projected on an inflated surface rendering of the human brain using the CARET program (Van Essen et al., 2001).

A linear mixed effects model was used to evaluate whether the increased activity in these areas was related to a participants ability to ignore irrelevant targets. The model included fixed effects for age, distraction cost ( $RT_{IT-NT}$ ) and brain area and a random intercept per subject. The results indicated that increased activation in specific brain areas was associated with a larger distraction costs; that is a larger difference in response times between IT and NT trials ( $RT_{IT-NT} * \text{area } F(8,549)=4.7, p < 0.001$ ; see figure 7.3). These effects were found specifically in the right middle occipital gyrus ( $t(61)=3.02, p=0.004$ ), the right superior parietal gyrus ( $t(61)=2.42, p=0.019$ ), the left superior parietal gyrus ( $t(61)=2.57, p=0.0125$ ), the left inferior parietal gyrus ( $t(61)=3.42, p=0.0011$ ) and the left frontal eye fields ( $t(61)=2.22, p=0.03$ ).

We additionally tested whether connectivity strength between each of these DAN areas was associated with age and distraction cost. Fixed effects in the model included age and  $RT_{IT-NT}$ . Because of the large number of area combinations (36), the area pairs were not modeled as fixed, but as random effects, in addition to the random intercepts for subjects. Separate models were constructed for overall connectivity strength and the change in connectivity strength in IT compared to NT trials. To examine whether the observed relations between connectivity, age and distraction cost were specific for task execution, we tested connectivity during a period of eyes closed resting state in a separate model. During task performance, average connectivity was smaller in old than young participants ( $F(1,61)=18.79, p < 0.001$ ). Increased connectivity in the DAN tended to go along with increased distraction cost, although this was not significant ( $F(1,61)=3.50, p=0.066$ ). The connectivity values averaged over all areas were significantly

higher in IT than NT trials ( $t(64)=2.22$ ,  $p=0.03$ ). This connectivity increase tended to be related to increased distraction cost in young, but not older participants, although this was not significant (interaction:  $F(1, 61)= 7.53$ ,  $p=0.008$ ; young:  $F(1,28)=3.76$ ,  $p=0.063$ ; old:  $F(1,33)=0.69$ ,  $p=0.41$ ). During resting state, connectivity was also higher in younger than older participants ( $F(1,59)=8.91$ ,  $p=0.004$ ) and increased connectivity was related to increased distraction cost ( $F(1,59)=5.31$ ,  $p=0.025$ ).

When no global signal regression was applied on the resting state data, the effect of age on connectivity remained significant ( $F(1,59)=6.37$ ,  $p=0.014$ ), however, there was no longer a relation between distraction cost and connectivity.

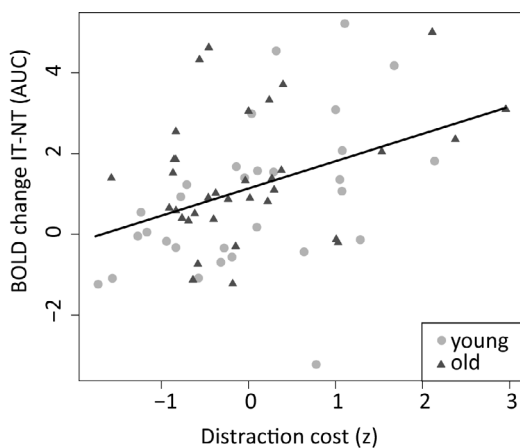


Figure 7.3: Relation between distraction cost ( $RT_{IT-NT}$ ) and changes in BOLD (IT-NT) in the left inferior parietal lobule.

To check whether this activation difference between IT and NT trials was in fact related to interference from a salient irrelevant stimulus, as opposed to the presence of a target letter in the display which attracts attention, we additionally compared IT to T trials. The areas active in this contrast were very similar to the IT - NT contrast (see figure 7.4 and table 7.3). Increased activation in IT versus T trials was observed in the right and left middle occipital lobule all the way up to the bilateral inferior and superior parietal lobules. In addition, the bilateral inferior temporal gyrus, the anterior cingulate cortex, the bilateral inferior frontal operculi and the right middle frontal gyrus, extending into the FEF were more active in IT than T trials. Increased activation in T compared to IT trials was observed in the left postcentral gyrus.



Table 7.3: Areas in which BOLD activation changed significantly ( $P_{FWE} < 0.05$ ) in irrelevant target, compared to target trials.

Irrelevant targets > Targets	k	T	x,y,z (MNI)
R Sup Parietal (BA 7)	3626	8.96	28 -56 50
R Inf Frontal Operculum (BA 44/48)	4694	7.57	40 14 30
L Mid Occipital (BA 19)	4143	7.51	-36 -84 12
L Inf Frontal Operculum (BA 44/48)	1202	6.73	-38 10 26
R Inf Temporal (BA37)	741	6	46 -56 -12
R Ant Insula (BA 47)	310	4.83	32 24 -2
Targets < Irrelevant targets			
L Postcentral (BA 3)	638	4.89	-52 -20 46

L=left, R=right, BA=Brodmann's area, x,y,z=stereotactic coordinates, k=cluster extent, Mid=middle, Inf=inferior, Sup=superior, Ant=anterior.

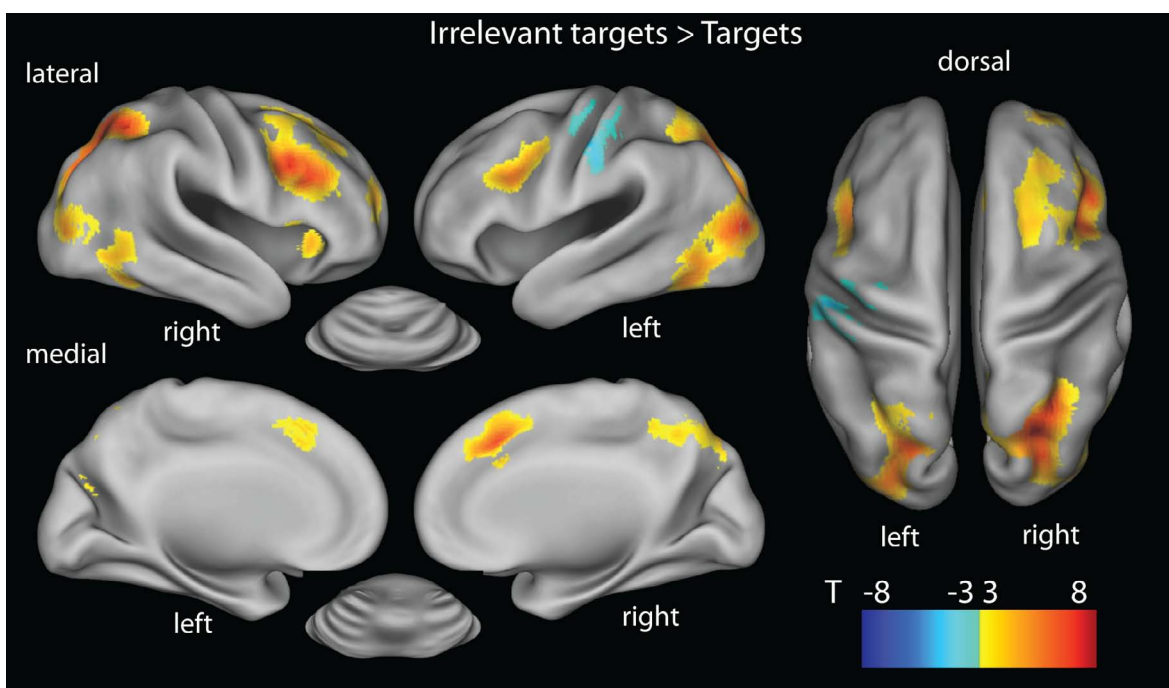


Figure 7.4: Areas which were more active (yellow-red) or less active (green-blue) in irrelevant target compared to target trials.

### 7.4.3 Targets versus nontargets

In target trials compared to nontarget trials, participants had more activation in areas related to somatomotor functions, the right and left pre- and postcentral gyrus and the right cerebellum (see figure 7.5 and table 7.4). There were four areas where activity was significantly decreased in T versus NT trials; the right middle cingulum, the right inferior frontal triangular area, the left inferior frontal operculum and the right superior frontal gyrus. In addition to these areas activated in both age groups, there were a number of areas which were significantly more active in the older compared to the younger group ( $T > NT$ ). These included the right postcentral gyrus, the right rostralateral PFC (RLPFC),



the left and right inferior parietal/angular gyrus, the dorsolateral PFC (DLPFC) and the left cerebellum crus2 (see figure 7.5).

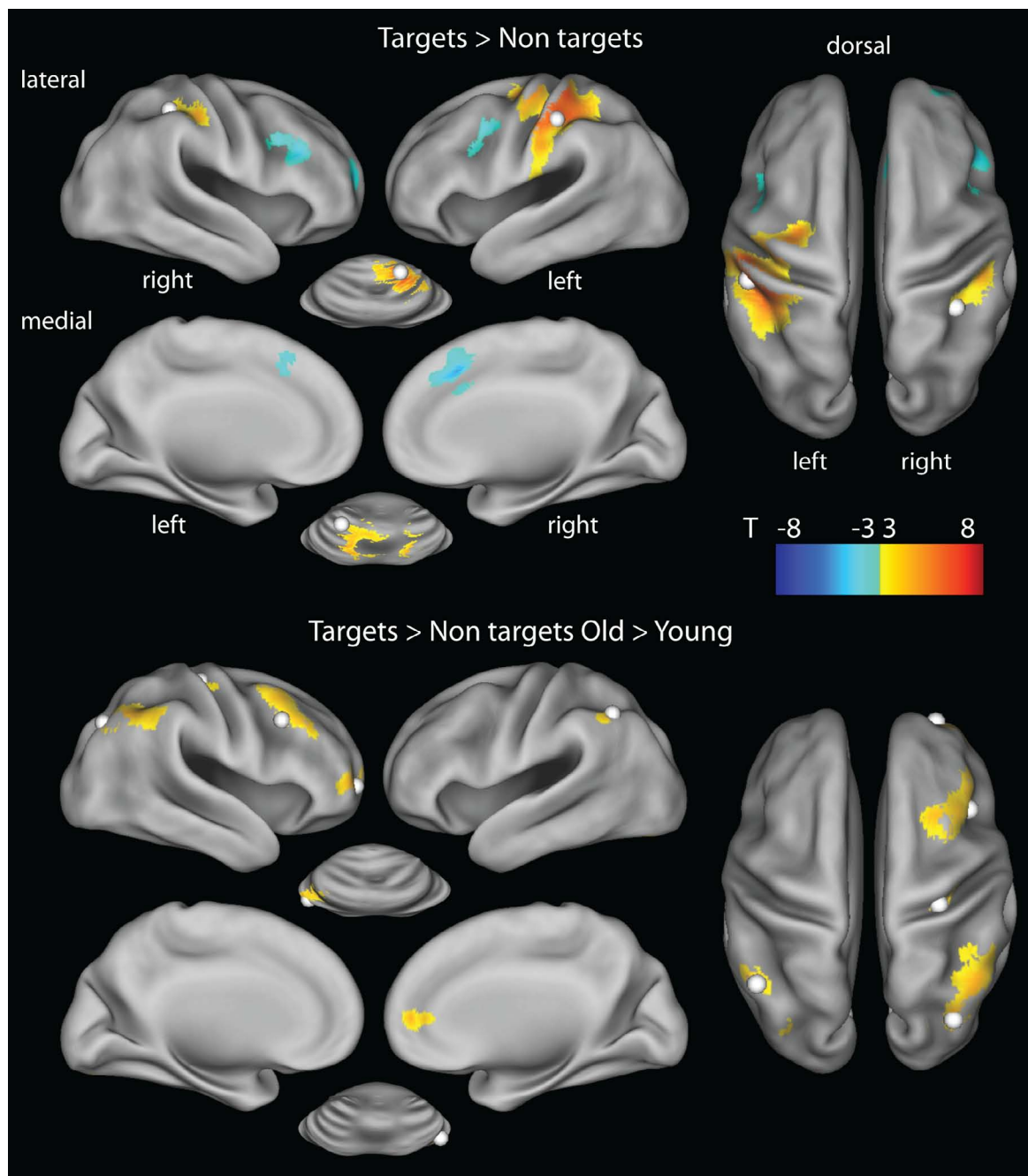


Figure 7.5: *top* Areas which were more active (yellow-red) or less active (green-blue) in target compared to nontarget trials. The white spheres indicate the centers of the associated ROIs projected on the surface. *bottom* Areas in which the difference in activation between target and nontarget trials was larger in older than in younger participants.

Table 7.4: Areas in which BOLD activation changed significantly ( $P_{FWE} < 0.05$ ) in target, compared to nontarget trials.

Target > Nontargets	k	T	x,y,z (MNI)
L Inf Parietal / Postcentral (BA 3)	3214	7.52	-48 -26 48
R Cerebellum 6	991	7.1	20 -54 -22
R Postcentral (BA 40)	661	5.84	32 -34 46
R Cerebellum 8	580	5.02	24 -62 -52
Targets < Nontargets			
R Middle Cingulum (BA 32)	783	5.64	8 24 40
R Inf Frontal Triangular (BA 48)	386	4.76	50 24 26
L Inf Frontal Operculum (BA 48)	314	5.51	-36 6 26
R Sup Frontal (BA 10)	331	4.68	26 54 10
Targets > Nontargets Old > Young			
R Postcentral (BA 3)	347	5.27	28 -26 52
R Mid Orbitofrontal (BA 11)	1071	4.85	28 52 -4
R Angular / Inf Parietal (BA 7)*	1095	4.86	36 -72 42
R Dorsolateral PFC (BA 44)	910	4.67	42 18 38
L Inf Parietal (BA 39/40)	315	4.75	-46 -58 48
L Cerebellum Crus 2	688	4.56	-34 -70 -38

L=left, R=right, BA=Brodmann's area, x,y,z=stereotactic coordinates, k=cluster extent

\* indicates the area in which the activation increase (T>NT) was related to decreased ACC detection cost ( $ACC_{NT-T}$ )

To test the relation between activity in these areas and the detection effect, separate linear mixed effects models were constructed for the areas involved in the main effect and the areas involved in the interaction effect. Fixed factors included age, RT detection effect ( $RT_{T-NT}$ ), ACC detection effect ( $ACC_{NT-T}$ ) and brain area. In addition, a random intercept per subject was included. As the correlation between ACC detection effect and RT detection effect was low ( $r=0.10$ ) we did not orthogonalize these regressors prior to the analysis. Interactions between ACC detection effect and RT detection effect were not included in the model. For the somatomotor areas showing the main effect of T>NT there was no significant relation between the activation increase (T>NT) and RT detection effect or ACC detection effect. For the FPCN areas showing the interaction effect age\*T>NT, there was an interaction between brain area and ACC detection effect ( $ACC_{NT-T}$ ;  $F(5,295)=2.49$ ,  $p=0.031$ ). When following up this effect, we found that increased brain activity in the right inferior parietal lobule was related to a decreased ACC detection effect ( $t(61)=2.27$ ,  $p=0.027$ ; see figure 7.6).

Connectivity was computed separately in three connectivity categories (CC); connectivity between the somatomotor areas showing a main effect of T>NT (CC-motor), connectivity between the FPCN areas showing an effect of T>NT only in the older adults (CC-FPCN) and connectivity between the somatomotor and FPCN areas (CC-motor-FPCN). If the age-related increase in FPCN activation actively improves performance (T>NT), then an increase in connectivity is expected between regions in the FPCN and the somatomotor areas showing a main effect of T>NT. This would be reflected in an age-related increase in connectivity in CC-motor-FPCN. In the linear mixed effects model, CC (3 levels; CC-motor, CC-FPCN and CC-motor-FPCN) was entered as a fixed effect (with

CC-motor-FPCN as the intercept), along with age, RT detection effect ( $RT_{T-NT}$ ) and ACC detection effect ( $ACC_{NT-T}$ ). Random effects included a random intercept per subject and a random intercept for each area. The areas were not modeled as separate fixed effects because of the large combination of area pairs.

During task performance, connectivity was different in the three connectivity categories ( $F(1,42)=5.34, p=0.009$ ). On average, connectivity was higher in CC-motor than CC-FPCN ( $t(128)=2.73, p=0.007$ ), and higher in CC-FPCN than in CC-motor-FPCN ( $t(101)=10.65, p<0.001$ ). Effects of connectivity type were modulated by age group ( $F(1,2804)=92.24, p<0.001$ ). Compared to young participants, older participants showed increased connectivity in CC-motor-FPCN ( $F(1,59)=42.83, p<0.001$ ). Decreased connectivity in older compared to young participants was found within CC-motor ( $F(1,59)=17.27, p<0.001$ ) and CC-FPCN ( $F(1,58)=24.47, p<0.001$ ).

In addition, we found that the relation between connectivity and the ACC detection effect was different for the three connectivity categories ( $F(1,2804)=13.62, p<0.001$ ). For CC-motor-FPCN, increased connectivity was related to a decreased ACC detection effect ( $F(1,59)=4.22, p=0.044$ ). However, for the CC-FPCN, increased connectivity was related to an increased ACC detection effect ( $F(1,59)=5.74, p=0.0198$ ). Note that, although the interaction is not significant, the latter relation was driven by the younger participants (interaction:  $F(1,59)=3.49, p=0.067$ ; young:  $F(1,27)=6.31, p=0.018$ ; old:  $F(1,32)=0.37, p=0.54$ ).

On average there was no significant change in connectivity strength in T versus NT trials for any of the CC categories. No relation between the connectivity change in T versus NT trials and age or performance was found.

To test whether these effects were specifically related to task performance, we investigated these same effects during resting state (these are the data in which global signal regression was applied). There we found a similar effect of age on connectivity as during task performance. Similar to the effect of age on connectivity during task, there was an interaction between age group and CC-category ( $F(2,2716)=29.6, p<0.001$ ); younger adults had higher connectivity than older adults in CC-motor ( $F(1,57)=10.11, p=0.002$ ) and CC-FPCN ( $F(1,57)=10.44, p=0.002$ ), whereas older adults had higher connectivity in CC-motor-FPCN ( $F(1,57)=6.82, p=0.011$ ). In addition, in older but not younger participants, increased connectivity in the CC-motor-FPCN was associated with a decreased ACC detection effect ( $F(1,31)=5.01, p=0.033$ ). It should be noted though, that in the analysis with both age groups together, no significant main or interaction effect was observed.

When this analysis was repeated without global signal regression, the same age-related decline in connectivity within CC-FPCN and CC-Motor was observed (interaction:  $F(2,2716)=24.8, p<0.001$ ; CC-FPCN:  $F(1,57)=12.01, p=0.001$ ; CC-motor  $F(1,57)=7.81,$

$p=0.007$ ). The age-related connectivity increase in CC-motor-FPCN was not observed anymore. In addition, the increased connectivity in the CC-motor-FPCN was no longer associated with a decreased ACC detection effect in older participants, but with an increased ACC detection effect in young participants ( $F(1,26)=5.13$ ,  $p=0.032$ ).

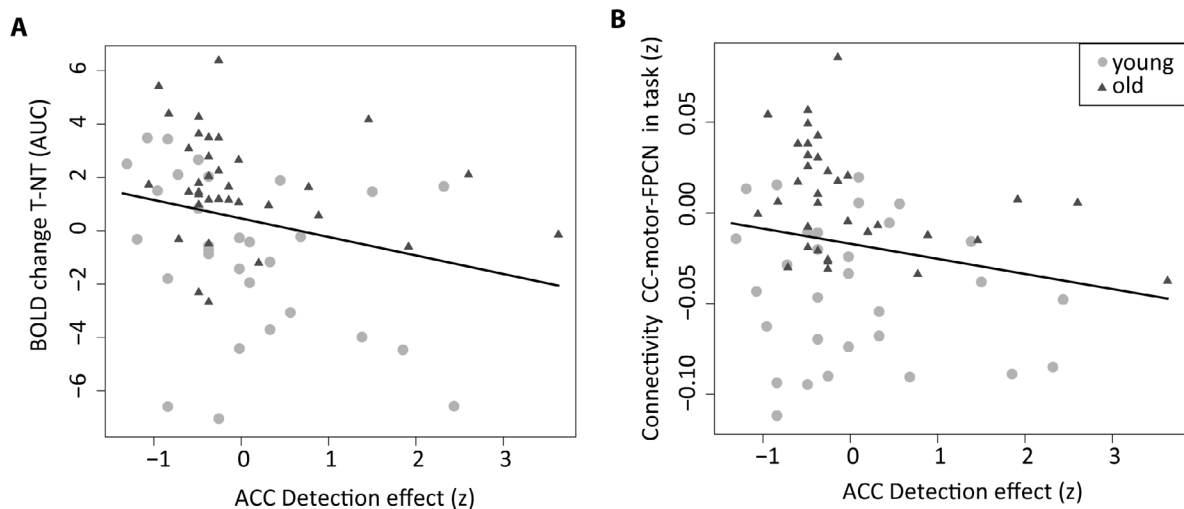


Figure 7.6: **A** Relation between ACC detection effect and BOLD change between T and NT trials. **B** Relation between ACC detection effect ( $ACC_{NT-T}$ ) and overall connectivity strength in CC-motor-FPCN.

## 7.5 Discussion

The behavioral data are in agreement with previous research, suggesting that older adults show deficits in suppression of irrelevant information, while enhancement of relevant information is not affected by age (de Fockert et al., 2009; Gazzaley et al., 2005a; Mager et al., 2007). Both age groups showed an increase in response times in irrelevant target compared to nontarget trials. This indicates that participants were not able to focus selectively on information on the relevant diagonal, resulting in distraction by the target stimulus appearing on the irrelevant diagonal. This effect was larger in the older participants, indicating a deficit in suppression of irrelevant information. Whereas both age groups were less accurate in target compared to nontarget trials, this effect was smaller in the older group. Moreover, older participants were faster in target trials compared to nontarget trials, while younger participants were slower. These effects suggest that older participants may even outperform younger participants in the processing of relevant information.

Possibly, the age-related differences in the performance on target compared to nontarget stimuli are related to differences in response tendencies. It is known that there

are marked differences in the tradeoff between speed and accuracy in older and younger participants (Forstmann et al., 2011; Rabbitt, 1979). Even at the cost of very high response times, older participants in general avoid errors (Starns & Ratcliff, 2010). In the current task, 66% of the stimuli required the same response. Therefore, to optimize speed, it would be efficient to prepare for that most frequent response prior to stimulus onset. Then, when a target is detected at a relevant location, participants can switch the response. It has been shown in literature that suppression of a prepotent response is associated with an increase in error rates and increased response times to the non-prepotent response (Madden et al., 2004; Nieuwenhuis et al., 2003). A closer inspection of the response time and accuracy data of the young participants, suggests that this strategy was indeed applied. The young participants were both slower and less accurate in target compared to nontarget trials. This pattern of results is markedly different from those observed in previous studies using a similar task, in which it was demonstrated that participants are generally faster in target compared to nontarget conditions when both response categories are equally prevalent (Shiffrin & Schneider, 1977).

In accordance with the large body of literature that has shown that older adults favor accuracy over speed, we found that the older adults did not use the information about prevalence of certain stimuli to bias their response tendencies to optimize speed. They were actually faster during target compared to nontarget trials, similar to the pattern observed when the two response categories have equal probability (Shiffrin & Schneider, 1977). In addition, they were more accurate than younger adults during target trials. Whereas it might be suggested that this finding is at odds with the reported age-related decline in response inhibition, previous studies have also found that older adults make a comparable numbers of or even fewer errors than young adults in go/no-go task situations in which a prepotent response needs to be suppressed (Rush et al., 2006; Sebastian et al., 2013).

In the fMRI data, we observed that both younger and older participants activated primarily left and to a lesser extent also right (pre) motor and somatosensory areas more in target compared to nontarget trials. The pronounced left lateralization of this activation suggests that it is related to the required right hand response. Therefore, the increased (pre) motor and somatosensory activation in target compared to nontarget trials is in line with the idea that the less frequent response to target trials requires the participants to switch the response from the prepared response. Previous studies have found similar activation patterns in relation to a response switch. In an oddball task, infrequent target stimuli, requiring a switch from the most frequent response, activated the motor cortex to a much larger extent than infrequent novel visual stimuli that did not require a response switch (Madden et al., 2004). Based on our interpretation of the behavioral results, we would expect that the sensorimotor activation in trials would be less pronounced in older compared to younger participants. It is not clear why such a difference was not observed.



In addition, in target compared to nontarget trials, older participants showed increased activation in areas corresponding to the main components of the FPCN. Previous studies have also shown enhanced levels of activation in the FPCN in older adults, especially in the DLPFC and the RLPFC (Spreng et al., 2010b). If these areas are actively involved in supporting task performance, we would expect to find that increased activation in the FPCN areas, supporting cognitive control, would be related to increased performance. In addition, we would expect that increased connectivity between the FPCN and the somatomotor areas would be implicated in response selection and execution in older compared to younger participants. This is exactly the pattern that we found. Increased activity, specifically in the right inferior parietal lobule in target compared to nontarget trials, was related to reduced ACC detection cost, suggesting that this additional activation was indeed facilitating performance in older adults. Moreover, we found that while connectivity was decreased in older adults between areas within the FPCN and between areas within the somatomotor network, connectivity between the FPCN and somatomotor network was increased. These results support the presence of active compensatory mechanisms in older adults, which are likely to be related to the strategy differences between older and younger adults in performance of this task. The increased connectivity during task performance is not a side effect of increased overall activity within the FPCN in older adults, as connectivity between areas within the FPCN was actually reduced in the older compared to the younger group. Important evidence for the interpretation of compensatory FPCN function in older adults was provided by the relation with behavioral data. Those participants with higher connectivity between the FPCN and somatomotor areas showed a smaller decline in accuracy in target compared to nontarget trials. We found indications that the effects of age on connectivity were not specific to task execution, as a similar increase in connectivity between FPCN and somatomotor areas was observed in resting state. In addition, also in resting state increased connectivity between the FPCN and the somatomotor network was related to reduced ACC detection cost. This might suggest that the increases in between network connectivity that we observed before in older adults (Geerligs et al., 2012a) can be beneficial for performance on specific tasks. It should be noted however, that these effects were no longer present when no global signal regression was applied, therefore these data should be interpreted with caution.

Older adults have more trouble with the enhancement of relevant information, in the context of other irrelevant stimuli (Chee et al., 2006; Quigley et al., 2010). Therefore, the increased involvement of the FPCN areas in older adults in target trials might signal the use of additional reactive control processes which support the adequate detection of target stimuli in this group (Braver et al., 2009). This is in line with a previous study on auditory target detection that has found that older adults use controlled processing to compensate for reduced levels of automatic processing of target stimuli (Alain et al., 2004). However, an alternative explanation could be that the increased recruitment of the FPCN in older adults is related to higher levels of control over the response, which in turn may

be related to the tendency of older adults to avoid errors irrespective of the speed costs (Starns & Ratcliff, 2010). It is important for future studies to disentangle the two possible explanations. However, regardless of the underlying mechanisms, the current findings demonstrate that older adults use additional recruitment of the FPCN as a compensation mechanism to enable good performance in detection of or response to target stimuli, as reflected in a decreased number of errors.

In contrast to the age-related enhancement of activity in the FPCN during target versus nontarget trials, we found no age-related changes in activity in this network elicited by irrelevant target information. Instead, both age groups areas activated in the IT compared to the NT condition correspond to those belonging to the dorsal attention network (DAN). Both older and younger participants showed an association between increased distraction by irrelevant information and larger DAN activity. Similarly, the connectivity increases between DAN areas in IT compared to NT trials were also related to increased distraction.

Areas in the DAN have been related to (re-)orienting of attention by top-down processes (Buschman & Miller, 2007; Corbetta & Shulman, 2002; Corbetta et al., 2008). This reorientation can be driven by the task goals or by the detection of salient stimuli by the bottom-up oriented ventral attention network (Corbetta et al., 2008). Based on these findings, one could argue that the observed increase in activation in the DAN could reflect the orientation of attention to salient (irrelevant) target stimuli, triggered by the ventral attention network. However, this explanation is unlikely because the same DAN areas are more active when we compare irrelevant target to target trials, which both contain a target stimulus. Therefore, it is more likely that these DAN areas are involved in resolving the interference caused by the irrelevant information, for example by reorientation of attention from the irrelevant target to the stimuli on the relevant diagonal or disengaging attention from the irrelevant target stimulus. These results show that an increased reliance on resolution of interference after stimulus onset (reactive control) is related to slowing of response times. Increased connectivity between the DAN areas was also related to increased distraction cost during resting state. This might indicate that in individuals who generally rely on reactive control strategies because of insufficient proactive control, the connectivity in the DAN network is strengthened. It should be noted however, that these results should be interpreted with caution as the relation between distraction cost and connectivity in resting state was only present when global signal regression was applied.

The fact that no age-difference was observed in the contrast between irrelevant target and nontarget stimuli, is in line with previous results by Gazzaley and colleagues (2008), who showed that there is no age-related impairment in suppression of irrelevant information in later stages of processing. In addition, no evidence was found for the employment of additional reactive control mechanisms in older adults to overcome the deficit in suppression of irrelevant information in early stages of processing (de Fockert et



al., 2009; Haring et al., 2013; Schmitz et al., 2010).

In conclusion, we confirmed that older adults indeed have a deficit in the suppression of irrelevant information, while enhancement of relevant information was not impaired. In both older and younger participants, the distraction cost elicited by irrelevant targets, appears to be related to an increased need for top-down (re-) orientation of attention, as reflected by connectivity and activity increases in the DAN. To detect and respond adequately to target stimuli, older adults appear to employ additional cognitive control processes to enable optimal performance, as reflected by additional activity in the FPCN and the increased connectivity between the FPCN and the somatomotor network.



# Chapter 8

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General discussion and future perspectives

## 8 General discussion and future perspectives

The current thesis aimed at gaining knowledge on age-related changes in the relation between cognition and brain function. In particular, the focus was on integration of information between different brain regions and brain networks. A lot of research in the past decades has focused on identifying the functional role of numerous brain areas. With this knowledge, it is now possible to study how these areas work together to accomplish the transformation of the sensory input the brain receives to the behavioral response that follows. In this thesis we used this new avenue in the study of brain function to understand the mechanisms underlying age-related changes in cognitive functioning. In the first part of this thesis (chapters 2-4) we examined connectivity in the entire brain to establish how the integration of information changes in old age, both during task performance and resting state. In addition, we linked individual differences in connectivity to individual differences in cognitive functioning. In the second part of the thesis (chapters 5-7), we zoomed in on one specific cognitive function; selective attention. There, we aimed to deepen our understanding of how age-related changes in this specific ability could be related to changes in functional connectivity during task performance. In this chapter, the main findings of all studies are summarized and integrated and critical considerations as well as future directions are discussed.

### 8.1 Effects of aging on functional connectivity

Aging equals change. Previous research has shown that functional connectivity is affected by aging and that changes in functional connectivity might be related to declines in cognitive functioning (Andrews-Hanna et al., 2007; Rieckmann et al., 2011; Sambataro et al., 2010; Voss et al., 2010; Wu et al., 2007). Therefore, in the first part of this thesis we have studied the nature and extent of age-related changes in functional connectivity. Most research so far has been limited to studying age-related changes within specific functional networks (Andrews-Hanna et al., 2007; Rieckmann et al., 2011; Sambataro et al., 2010; Voss et al., 2010; Wu et al., 2007). In the set of studies described here, we aimed to get a more complete picture of the effects of aging on connectivity within as well as between networks. Using different analysis techniques (chapters 2, 3 and 4), we demonstrated that aging is indeed associated with large-scale changes in functional network connectivity. Although we found some differences between our studies, the overall pattern that emerged was that connectivity within specific functional networks decreased (chapter 2 and 3), whereas connectivity between (specific) functional networks increased with age (chapter 2, 3 and 4).

In chapter 2, we studied the effects of aging on connectivity within and between functional networks using a combination of seed-based connectivity analysis and k-means cluster analysis. The striking observation in this study was that age-related

increases in connectivity from a particular seed region were generally located outside of the functional network the seed region belonged to. In contrast, the age-related decreases in connectivity from a particular seed region were generally located within the functional network the seed region belonged to. These results were the first indication that changes in connectivity within as well as between functional networks are an important feature of aging. More specifically, we found that connectivity within the default mode network (DMN) and the somatomotor network declined with age. In addition, all identified networks showed increased connectivity to other functional networks. The net result of these changes in functional connectivity is that the functional networks become less distinct in older compared to younger adults.

In chapter 3, we set out to study these age-related changes in functional connectivity in more detail. While brain activity was recorded during task performance in chapter 2, in chapter 3 we measured brain activity during resting state. In chapter 3 we used a novel technique to study changes in functional connectivity; graph theory (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010). Using graph theory, we were able to quantify age-related changes in terms of several complex network measures. In a graph, brain areas are referred to as nodes, whereas connections between brain areas are edges. To test whether functional networks are really becoming less distinct in older adults, we examined changes in modularity. Modularity is a measure of the extent to which a graph can be divided into separate networks with a maximal number of within network connections and a minimal number of between network connections (Girvan & Newman, 2002). We found that there was indeed a substantial decrease in modularity in the older compared to the younger participants.

To examine the origin of this age-related decrease in modularity on a more local scale, we additionally studied the network measures local efficiency and participation coefficient. Local efficiency is a measure of information integration on a local scale and the local resilience of a network against the loss of nodes (Latora & Marchiori, 2001). The participation coefficient is a measure of the proportion of between network connections compared to within network connections from each node in the network (Guimerà & Amaral, 2005). Using these two measures, we found a striking dissociation. The networks involved in more basic sensorimotor functions, that is the visual network and the somatomotor network, showed an increase in participation coefficient in older compared to younger adults, indicating that nodes in these networks had increased connectivity to nodes in other functional networks. In contrast, the local efficiency was decreased in older adults, in networks involved in higher order cognitive processes. These networks were the DMN, the fronto-parietal control network (FPCN) and the cingulo-opercular network. This finding indicates that connectivity within these networks was reduced in older compared to younger adults.

In chapters 2 and 3, we established that connectivity changes are a major factor in the

effect of aging on brain function. Therefore, in chapter 4, we went one step further by investigating whether older adults are still able to flexibly adapt functional connectivity to the demands of the task at hand. Connectivity between functional networks was assessed during resting state (same data as chapter 3), during a selective attention task and during a working memory task in the same participants. Independent component (IC) analysis was used to identify the different functional networks in a data-driven way. Here, we did not only examine the adaptations of connectivity to task demand, but we also investigated the 'main' effects of aging on connectivity between different functional networks. In all three task conditions we found that in older participants, connectivity to other functional networks was increased. This was true for visual ICs, the cerebellar IC, the basal ganglia IC, the bilateral somatomotor IC and the anterior cingulate IC.

Using different methodological approaches in each of the studies described in chapters 2-4 and by examining different task conditions, we were able to get a more complete picture of the age-related changes in functional connectivity. Moreover, by using these complementary approaches, we have shown that the changes in functional connectivity are general and can be shown largely independent of specific methods or task conditions. In addition, recent studies by other groups, using different methods, have also show the same pattern of increased connectivity between networks along with decreased connectivity within networks (Meier et al., 2012; Tomasi & Volkow, 2012; Voss et al., 2010). The strong correspondence between all of these results establishes that increased connectivity between networks, along with decreased connectivity within networks is a stable pattern of age-related changes that can be observed in different groups of older adults during task performance as well as during resting state.

### 8.1.1 Dedifferentiation

The net result of the observed age-related connectivity changes is that the boundaries between functional networks are fading in older adults; the distinctiveness of functional networks decreases with age. This finding is in line with the dedifferentiation theory that suggests that areas in the older brain may become less functionally distinct (Baltes & Lindenberger, 1997; Carp et al., 2011a; Dennis & Cabeza, 2011; Park et al., 2004). Carp et al. (2011a) demonstrated the extent of dedifferentiation in a recent study using multi-voxel pattern analyses. They showed that the activation patterns of distinct visual stimuli showed a larger overlap in older than younger adults. Importantly, these effects of aging were not limited to representations in the visual cortex but extended to parietal and frontal areas, as well. Possibly, dedifferentiation of brain areas and dedifferentiation of brain networks are two sides of the same coin. The reduced functional specialization of brain areas might result in increased functional connectivity to a larger number of other brain areas, thereby causing dedifferentiation of functional networks. In addition, the increased functional connectivity between brain areas in different functional networks

could cause these brain areas to be activated in response to the same stimuli, thereby causing dedifferentiation of brain areas.

There is only little knowledge on how dedifferentiation is related to cognitive functioning in older adults. Previous research by Park and colleagues (2010) has shown that decreased functional specificity of brain areas was related to decreased measures of fluid, but not crystallized intelligence in older adults. Their finding suggests that dedifferentiation might indeed be related to age-related changes in cognitive functioning. In chapter 3, we studied how individual differences in modularity, which can be interpreted as a measure of differentiation in functional networks, might be related to differences in cognitive functioning between individuals as measured with a large battery of neuropsychological tests. Using this approach, we did not find a direct link between dedifferentiation and cognitive functioning.

Summarizing, in the first part of this thesis we have demonstrated that dedifferentiation does not only occur on the level of brain areas (Park et al., 2004), but also on the level of brain networks. Dedifferentiation might be one mechanism underlying age-related declines in cognitive functioning, however more research is needed on the link between dedifferentiation and cognitive functioning to test this possibility.

### 8.1.2 Compensation

An important question is whether the observed age-related changes in functional connectivity reflect active adaptation (compensation) or passive change. In the second part of this thesis, we have studied how individual differences in functional connectivity during a selective attention task relate to differences in task performance. We found that specific increases in functional connectivity were related to better performance in the older group whereas no relation with performance was observed in the group of young participants. More specifically, in chapter 5, increased EEG connectivity between occipitoparietal and frontal electrodes in the beta band was related to an increased ability to suppress irrelevant information. In chapter 7, increased connectivity between the FPCN and somatomotor areas was related to more accurate detection of target stimuli in older adults. These results demonstrate that in specific tasks, increased functional connectivity can have a compensatory function in older adults.

It is unclear whether the changes in connectivity between networks as observed in chapters 2, 3 and 4 also have a compensatory role. In both chapters 2 and 3, we found that the decreased connectivity within functional networks was related to decreased cognitive functioning. Therefore, it is possible that increased connectivity between networks is mitigating these effects of decreased connectivity within networks. However, no clear relations were found between enhanced cognitive functioning and the increased



connectivity between networks. This raises the question what the mechanisms could be that cause age-related changes in functional connectivity.

### 8.1.3 Underlying mechanisms

The most likely underlying mechanism for age-related changes in functional connectivity is age-related changes in brain structure. As was discussed in chapter 3, the networks that exhibit age-related decreases in functional connectivity have quite some overlap with the brain areas that generally show age-related decreases in grey or white matter integrity. In chapter 2, we explicitly examined whether age-related changes in functional connectivity could be explained by reductions in gray matter volume. Although the effects of aging on functional connectivity were reduced when corrections for gray matter volume were taken into account, differences between age groups in within as well as between network connectivity remained. This suggests that changes in gray matter alone cannot explain the functional connectivity changes observed in the aging brain.

In young adults, several studies have found a positive relation between structural connectivity and functional connectivity (Honey et al., 2009; Skudlarski et al., 2008; van den Heuvel et al., 2008). For example, Honey et al (2009), showed that, depending on the exact methods used, between 13% and 67% of the variation in functional connectivity could be explained by structural connectivity as measured by diffusion spectrum imaging. They showed that when structural connectivity is present between two areas, functional connectivity can be reliably inferred. However, when structural connectivity is minimal or absent the inference is much less reliable. Moreover, they found that functional connectivity is recurrently reconfigured around the underlying structural connectivity architecture. These results confirm that age-related structural connectivity changes could have a large impact on the observed functional connectivity changes. However, they also point to the flexibility of functional connectivity around the underlying fixed anatomical architecture.

Decreased dopamine functioning (Bäckman et al., 2010; Bäckman et al., 2006) could be another factor that contributes to age-related changes in functional connectivity. Rieckmann et al. (2011) showed that individual differences in dopamine receptor density in the caudate in young and older adults were related to connectivity between the DLPFC and the right parietal cortex. Li and colleagues (2001) proposed that the age-related decrease in dopamine functioning might lead to additional noise, defined as haphazard neuronal activity. This increase in neural noise might be the cause of the reduction in the specificity of neural representations with age. In a more recent simulation study, Deco and colleagues (2009) demonstrated that neural noise could impact the connectivity within and between functional networks. They showed that there is an optimal level of neural noise, at which correlations within networks and anticorrelations between networks are

highest. An increase or a decrease in noise with regard to this optimum reduces both correlations and anticorrelations (Deco et al., 2009). Therefore, an increase or decrease in neural noise could be directly related to the observed reduced distinctiveness of functional networks in older adults. The results above thus suggest that (part of) the age-related changes in functional connectivity might be the result of a cascade of changes in gray and white matter structure and neurotransmitter function.

#### 8.1.4 Flexible functional connectivity

In chapter 4 we found evidence that the changes in functional connectivity with age cannot be explained fully by changes in brain structure. In that study, we examined how functional connectivity is adapted to the demands of the task at hand. It has been shown that in young adults, connectivity within and between networks changes, depending on the task participants are performing (e.g. Dew et al., 2012; Hare et al., 2010; Sala-Llonch et al., 2012; Shirer et al., 2011; Sterpenich et al., 2006; Wolbers et al., 2006). Therefore, in chapter 4, we investigated whether older adults are still able to flexibly adapt functional connectivity to changing task demands. To this end, we examined how connectivity between different ICs changes between resting state, a selective attention task and a working memory task with varying levels of difficulty. We demonstrated that both younger and older participants are able to adapt functional connectivity to the demands of the task at hand. Importantly, older adults did so differently than young adults. While young adults showed the maximal change in functional connectivity with an increase in the level of task demand, older participants primarily showed a shift in connectivity between resting state and low demanding task conditions.

The results fit well with previous activation studies on age-related changes in adaptation to different levels of task demand. Mattay and colleagues (2006) showed that prefrontal activation was increased in older adults compared to younger participants in low working memory loads, whereas the opposite pattern was observed during high working memory loads. Following their compensation-related utilization of neural circuits hypothesis (CRUNCH), Reuter-Lorenz and Cappell (2008) suggested that processing inefficiencies cause the aging brain to recruit more neural resources to achieve computational output equivalent to that of a younger brain. This leads to overactivation of prefrontal brain areas at lower levels of task demand. At higher levels of task demand, older adults can reach a resource ceiling (Grady, 2012). Activity then no longer increases with increasing task demand and can even start to decrease again. In turn, this can lead to age-related declines in performance during more demanding tasks. Our results in chapter 4, demonstrate that this pattern of age-related change in resource recruitment is reflected in brain functional connectivity as well as brain activity.

## 8.2 Selective attention

The studies in the first part of this thesis focused on general age-related changes in functional connectivity between and within networks. In the studies described in the second part of this thesis, we looked at these changes on a different level, by studying how brain activity and brain connectivity are related to performance during a selective attention task in young and older adults. It is known that aging affects selective attention - the ability to enhance relevant information while ignoring or suppressing irrelevant information. In particular, older adults experience higher levels of interference from distracting, task irrelevant stimuli (Gazzaley et al., 2005a; Hasher & Zacks, 1988; Hasher et al., 1999). Previous studies that demonstrated age-related declines in the suppression of irrelevant information often used stimuli in which the relevant and irrelevant information overlapped in space or were segregated in time (e.g. de Fockert et al., 2009; Gazzaley et al., 2005a; Gazzaley et al., 2008; Quigley et al., 2010). This task design is quite different from situations in real life, in which relevant and irrelevant information are usually present at the same time in different spatial locations. Therefore, we used a task in which relevant and irrelevant stimuli were presented on the screen at the same time but in different locations. Participants were instructed to detect a pre-specified target letter in one of two pre-specified 'relevant' spatial locations. Only when a target letter appeared on a relevant spatial location, participants were instructed to answer by pressing a 'yes'-button. When only non-targets were presented (non-target condition) or when a target was presented on an irrelevant location (irrelevant target condition) they should press a 'no'-button. This task design is comparable to various situations in daily life, in which the target stimulus (i.e. a green light), should only be responded to when it is present at a specific spatial location (i.e. a traffic light). In chapters 5 and 7, the ability to suppress irrelevant information was expressed as the difference in response times between irrelevant target and non-target stimuli.

We found that not all older adults suffer from a decline in suppression of irrelevant information. In both studies there was a group of older adults who performed as well as the younger participants, whereas there was another group that did show a clear age-related decline. In line with previous studies on the effects of aging on cognitive functioning, we observed that the inter-individual differences in performance were larger in the older than in the younger group (Hultsch et al., 2002). Note that individual differences in the ability to suppress irrelevant information were not related to differences in processing speed. The influential, general slowing theory proposed that age-related changes in cognitive functioning result from a general decline in processing speed (Salthouse, 1991; Salthouse, 1996). However, our results show that at least part of the age-related decline in selective attention cannot be attributed to general slowing. The results do support the idea that a deficit in suppression of irrelevant information is an important factor in cognitive decline, in agreement with the inhibition deficit theory of aging (Hasher & Zacks, 1988).

In chapter 5, we investigated the neural mechanisms underlying the age-related deficit in suppressing irrelevant information using EEG. Already at very early stages of processing, individual differences in the ability to suppress irrelevant information were reflected in individual differences in the underlying neural processes. Especially older participants who showed a decline in the ability to suppress irrelevant information had a larger amplitude of the P1 component. This was interpreted to reflect increased processing of stimuli at irrelevant locations on the screen. Further evidence for an age-related decline in suppression of irrelevant information in early processing stages was obtained using time-frequency analysis. We found that after stimulus onset, alpha power was reduced in the older compared to the younger adults. Increased alpha power has consistently been related to increased inhibition (Jensen & Mazaheri, 2010; Klimesch et al., 2007). Therefore, the decline in alpha power might also reflect decreased suppression of information at irrelevant locations. Recent studies by other groups have also demonstrated that there is an age-related decline in suppression of irrelevant information in early stages of processing (de Fockert et al., 2009; Haring et al., 2013; Schmitz et al., 2010). Together, these results provide strong evidence that the decline in suppression of irrelevant information in (a subgroup of) older adults is due to deficits in early stages of processing.

### 8.2.1 Preparation for upcoming stimuli

In contrast to many previous studies, we have not only investigated differences in the neural signature of stimulus related processing, but we have also examined the role of preparation, as reflected in the neural activity prior to stimulus onset. Results show that preparation for upcoming stimuli might be especially important to enable adequate suppression of irrelevant stimuli at early stages of processing. In both young and older participants we found that increased phase locking in the alpha band between frontal and occipito-parietal electrodes was related to improved suppression of irrelevant information. Remarkably, this relation was only present prior to stimulus onset, indicating that increased alpha phase locking was related to preparation for the upcoming stimulus. Considering that alpha oscillations have been related to inhibition and top-down communication (Jensen & Mazaheri, 2010; Klimesch et al., 2007; Von Stein et al., 2000), the relation between pre-stimulus phase locking and processing of irrelevant information after stimulus onset might reflect the influence of top-down control. Alpha phase locking might reduce the excitability of the areas in the visual cortex in which the information on irrelevant spatial locations is processed, leading to increased suppression of irrelevant information after stimulus onset.

These results demonstrate that preparation for the upcoming stimulus (proactive control) can reduce the effect of irrelevant information on response times. In contrast, in chapter 7 we showed that when the interference caused by irrelevant target stimuli is resolved in a later stage of processing (reactive control), responses are slower. Participants

who showed the largest increase in activity and connectivity within the dorsal attention network (DAN) areas in response to irrelevant target stimuli, were the ones who showed the greatest slowing of response times in irrelevant- compared to non-target stimuli.

Together these findings suggest that in order to suppress irrelevant information, preparation for the upcoming stimulus is very important, whereas dealing with interfering stimuli at later stages of processing (reactive control) causes a decline in performance. Braver and colleagues (2009) proposed that older adults specifically suffer from a deficit in proactive control; the ability to actively prepare for upcoming stimuli. This idea is well in line with our findings. Age-related decline was especially observed in the early markers of attentional control (P1 and pre-stimulus alpha), which likely result from changes in pre-stimulus top down control. In addition, there are indications that older adults employ higher levels of reactive control in response to stimulus presentation. For example, older adults showed a substantial increase in alpha phase locking after stimulus onset. This could reflect the reduction of interference from irrelevant stimuli at a later stage of processing in older adults.

In chapter 5, we thus showed that the pre-stimulus brain state has a large impact on the processing of irrelevant target stimuli. In chapter 6, we demonstrated the extent of the influence the pre-stimulus brain state can have on the information processing. In that study, we asked participants to perform a temporal integration task, while EEG was recorded. They viewed two stimulus displays in rapid succession, which could be perceived as one stimulus (a grid of 24 squares) or as two separate stimuli (2 grids of 12 squares). Only when they perceived the stimuli as one stimulus, participants were able to detect the one square that was missing in the 5 by 5 grid of squares. By examining the time-frequency characteristics of trials in which participants were able to detect the missing square, compared to the trials in which participants were not able to detect it, we found a neural signature that predicted integrated perception on this task. Participants who had high levels of beta power prior to stimulus onset, were more likely to perceive the two stimuli as an integrated percept. These results demonstrate that the pre-stimulus brain state does not only impact the processing of irrelevant but also of task relevant information. In addition, it shows the extent of the influence the pre-stimulus brain state can have on information processing; it not only influences how participants respond to stimuli, but probably also how stimuli are perceived.

### 8.2.2 The role of compensation mechanisms in selective attention

The results described above indicate that individual differences in preparation and suppression of irrelevant information in early stages of stimulus processing might play an important role in the age-related decline of selective attention. However, in the second part of this thesis, we also found evidence that older adults can use compensatory

mechanisms to mitigate these effects of aging on selective attention. In chapter 5, we found that occipito-frontal phase locking in the upper beta band (21-30 Hz) was related to efficient suppression of irrelevant information, but only in older adults. This effect was present both before and after stimulus onset, in contrast with the effect of alpha phase locking on suppression which was only present before stimulus onset. Although not much is known about the function of beta oscillations, there are indications that they are related to attention, or high levels of cognitive control (Engel & Fries, 2010; Gross et al., 2004; Wróbel et al., 2007; Wróbel, 2000). In chapter 6, we argued that beta oscillations might be related to the preparation of the perceptual system to optimally process the upcoming stimulus. Because increased beta phase locking was related to better performance in older, but not younger adults, this suggests that increased beta phase locking can be perceived as a compensation mechanism employed by high performing older adults. This interpretation was supported by the relation we found between the time-frequency (beta phase locking) and ERP data (the P1 amplitude); older adults with higher beta phase locking had lower P1 amplitudes, indicating that processing of irrelevant stimuli was reduced. Moreover, older adults with high levels of pre-stimulus alpha phase locking also had higher levels of phase locking in the upper beta band, indicating that these different mechanisms to adequately deal with irrelevant information, were co-occurring in older adults. Possibly, increased beta phase locking was related to the enhancement of items on the relevant diagonal. This enhancement could serve to increase the distinction between relevant and irrelevant information, making it easier for older adults to suppress irrelevant stimuli.

In chapter 7, we further examined the effects of aging on the attention to task relevant stimuli. There, we found additional evidence for the occurrence of compensatory mechanisms in older adults. Whereas young participants made more errors when responding to infrequent target stimuli as compared to more frequent non target stimuli, this decline in performance was much smaller in older participants. Looking at brain activation and connectivity, we found a clear difference between age groups in the neural mechanisms enabling target detection. Whereas younger participants only activated sensorimotor areas to respond to the target stimulus, older participants also activated areas in the FPCN. Brain areas in the FPCN showed increased connectivity to brain areas in the sensorimotor network in older compared to young participants, supporting their role in adequate task performance. Moreover, we showed that the increased connectivity between the FPCN and sensorimotor areas in older adults was related to more accurate responses to target stimuli. In young participants, this relation was not observed. We therefore argue that this might be a reflection of age-related compensation. Because the activation differences reflect changes in processing after stimulus onset, these results are also in line with the suggestion that especially reactive cognitive control is employed in older adults to maintain high levels of performance.

These results in chapters 5-7 illustrate that the study of brain function can greatly



support our understanding of differences in behavior. Whereas in most studies no age-differences are observed in responding to relevant stimuli, the current results show that older adult recruit additional brain areas to achieve these such high levels of performance. These differences in neural mechanisms might also have implications for performance. For example, we could hypothesize that because of the additional recruitment in older participants, they might show signs of mental fatigue sooner than younger participants, which could have an effect on the level of sustained task performance. In addition, the results described above demonstrate the importance of combining multiple analysis techniques that provide different sources of information, to get a better understanding of how aging affects information processing. In chapter 5, this was done by combining information on induced (oscillatory power and phase locking) and evoked (ERP) changes in brain activity. In chapter 7, by combining measures of activity and connectivity to understand the link between the change in neural patterns and the changes in behavior.

### 8.2.3 Implications for daily life

Daily life is filled with distractions that interrupt ongoing activities. Advertisements on the side of the road, telephones ringing in the workplace, incoming e-mail on the computer and many more. The studies in this thesis have shown that older adults particularly have trouble ignoring these irrelevant stimuli (second part of the thesis). The results suggest that especially for older adults, it is important to limit the number of distractions in the home- and work situations. For example, an older worker could decide to check on new email messages only a few times per day and to limit the amount of clutter on the desk.

While the increased distractibility of older adults often has a negative impact on their functioning, it might be possible to use it to their advantage. Studies in the group of Hasher (Biss et al., 2013) have demonstrated that older adults have better recall of irrelevant, distracting stimuli that were presented during task performance than younger adults. Memory for future events could thus possibly be strengthened by presenting cues or even explicit messages in the environment. One possibility would be to show reminders of important information in a text display at the bottom of the television screen.

### 8.3 Critical considerations and future perspectives

There are a number of factors that make the study of the aging brain a challenging endeavor. Below, some of these factors will be discussed and ideas for future studies will be presented.



### 8.3.1 Population representative samples

In the studies reported in this thesis, we have investigated neural mechanisms underlying age-related declines in cognitive functioning. However, it is important to realize that there is larger inter-individual variability in the healthy older group than in the young adults. Therefore, the subset of older adults that we measured might not be representative for the entire population of older adults. The older adults who participated in our studies, responded to an advertisement in a local newspaper asking for research participants. In general, we observed that those individuals who responded and became our participants did not sit at home all day; they were active, highly educated and engaged older adults who wanted to contribute to research. Older adults who are less active in daily life might be less likely to volunteer for participation in scientific research. It has been shown that older adults with a higher level of education as well as both physical and non-physical activity tend to have higher levels of cognitive functioning (Fratiglioni et al., 2004; Hertzog et al., 2008). Therefore, it is probable that the group of older adults that participated in this study, is not the group of older adults that experience the largest effects of aging on cognitive functioning. This limitation applies to the vast majority of aging studies. Especially when participants are required to come to the lab for fMRI and EEG measurements, it might be difficult to motivate low-fit older adults to participate. Hence, it can be expected that the effects of aging on cognitive function as well as brain function in the population are more substantial than the effects we observed in the current studies. Especially the group of low-fit older adults would have a lot to gain from training interventions. It is important for future studies to investigate whether the brain mechanisms underlying age-related decline can be generalized to this low-fit group of older adults and whether this group would be able to benefit from training interventions.

### 8.3.2 Motivation

A striking difference we observed while collecting the data of our younger and older participants, was the difference in motivation between both groups. Although both groups were motivated to participate, the older participants tended to be more strongly motivated than the younger participants. During the measurements, older adults were less likely to complain about the duration or about the discomfort of the EEG cap than the young adults. Moreover, for the older adults it appeared to be especially important to perform the tasks as best they could. It cannot be ruled out that these motivational differences were reflected in the levels of task performance as well as in the differences in neural signatures we observed in both groups. However, it should be noted that the young participants were motivated as well, as they performed at or near ceiling level in the different tasks. A previous study that has looked into the effect of age-differences on motivation showed that especially in older adults, the motivation to do well, was strongly related to the amount of effort invested in task performance, whereas this relation was

not as clear in young participants (Ennis et al., 2013). On the one hand, the higher levels of effort invested by older participants could lead to better task performance. However, it could also cause older adults to tire more quickly, which could actually cause a decline in performance. In future studies, recording information about the invested effort during task performance, using, for example, pupil dilation (Beatty, 1982) or systolic blood pressure responsivity (Hess & Ennis, 2012) could provide valuable additional information to examine the effect of aging on cognitive functioning in relation to the effect of effort.

### 8.3.3 Error avoidance

Another difference in task performance in older compared to younger participants is in the tradeoff between speed and accuracy (Rabbitt, 1979). Younger participants tend to optimize this speed accuracy trade-off depending on task instructions and the feedback provided. Older adults on the other hand consistently set a pace that nearly eliminates all avoidable errors (Starns & Ratcliff, 2010). Different explanations have been proposed for this effect (Forstmann et al., 2011). One possibility is that it might be more difficult for older adults to adjust the speed-accuracy trade-off due to degeneration of white matter connections between cortex and striatum. The connectivity between both brain structures enables speeded responses; when the input from the cortex to the striatum increases, the striatum in turn decreases the inhibitory control of the output nuclei of the basal ganglia. This enables faster, but possibly premature responses. Another explanation for differences in the trade-off between speed and accuracy is that older adults are able to adopt more risky response strategies, but that they avoid adopting these strategies because the weakened cortico-striatal connections do not support tight control over the speed-accuracy trade-off. Therefore a small decrease in response time could lead to a large decrease in accuracy.

Regardless of the origin of these effects, the speed-accuracy trade-off differences between older and younger adults make it more difficult to draw conclusions about age-related changes, both in the behavioral domain as well as regarding the neural mechanisms supporting behavior. If two groups are not using the same strategy to accomplish a cognitive task, it becomes more difficult to attribute changes to either age-differences or strategy differences. Because older participants do not respond well to incentives to change the trade-off (Starns & Ratcliff, 2010), it is difficult to design an experiment where this effect would not play a role. Moreover, even at similar levels of speed versus accuracy, older and younger adults still differ in their trial-to-trial response time variability, indicating more conservative strategies in older participants (Smith & Brewer, 1995). In the current thesis, these differences in speed-accuracy trade-off were most apparent in situations of relatively low task demand, such as the selective attention task, in which older adults were able to achieve very high levels of accuracy at the cost of decreased speed. In chapter 7, we observed that older adults actually had higher

levels of accuracy than younger adults during the detection of relevant target stimuli. This accuracy increase was related to increased connectivity between sensorimotor and cognitive control regions. Possibly, this increase in connectivity reflects an increase in cognitive control over the motor response, to reduce the number of erroneous responses. Alternatively, the increased levels of cognitive control could be used to support selective attention mechanisms. It is important to keep in mind that these differences between younger and older adults in speed-accuracy trade-off can have effects on the observed age-differences in behavior as well as brain function.

#### 8.3.4 Cross-sectional studies

Most aging studies assess the effects of aging on cognitive functioning as well as brain functioning using a cross-sectional design. This approach is generally used because there are many practical and monetary issues involved when following older participants over a long time frame in a longitudinal study. However a cross-sectional approach also has its downsides. The most important problem is that differences between older and younger adults in cognitive functioning do not necessarily reflect age-related decline. They could also be the result of individual differences in intelligence or education already present at a younger age.

Another problem with a cross-sectional approach is the cohort effect. The young and older groups have been exposed to different experiences during their lifetime which can have an impact on differences observed between the two groups. For example, whereas all of the young participants that participated in our studies had extensive experience using the computer for leisure or work activities, there were some older adults who never used a computer before. It is likely that these differences affected the performance in both groups, at least during the training phase. Moreover, the majority of the younger participants were psychology students, who had more experience than the older participants in the testing situation. This could also influence the observed differences between both age groups. By training participants on the tasks prior to the experimental sessions, we have tried to mitigate the influence of these cohort effects. It should be noted that on average, the level of education was high in both the younger and the older participants.

Yet, the issues described above cannot be solved using a cross-sectional design. Therefore, it is important to replicate the results described in this thesis in longitudinal studies. In addition, longitudinal studies might provide more information about the mechanisms behind age-related changes in functional connectivity. First of all, changes in brain structure over time could be related more directly to changes in functional connectivity, thereby elucidating the interaction between the two. Second, the effects of functional connectivity changes on behavior could be clarified by investigating how

changes in functional connectivity over time relate to age-related changes in cognitive functioning over time. The combination of these approaches could also shed more light on the question whether age-related changes in connectivity should be interpreted as passive changes or active adaptations. This issue is particularly relevant in the context of the development of training interventions. If functional connectivity changes are indeed mainly the result of structural changes, there might be less room for improvement than if these changes would (partly) reflect active adaptations.

Because of the complexity of the brain's architecture, it is difficult to understand the consequences of specific changes in the brain or in behavior. Therefore explicitly modeling these changes could be an important tool to develop well defined hypotheses about the possible interactions between brain structure, brain function and behavior. By using network simulations, it becomes possible to look at the effects of declines in grey matter (loss of nodes), loss of white matter (loss of edges or loss of efficiency of edges) and increases in neural noise due to neurotransmitter functions on the structure of functional networks in the brain (Deco et al., 2009; Deco et al., 2012). Hypotheses generated with these techniques could subsequently be tested in cross-sectional as well as longitudinal studies.

### 8.3.5 Linking brain function and behavior - dynamics

In chapters 2, 3 and 4 we showed that there are large-scale changes in functional connectivity in older compared to younger adults. However, the implications of these changes for performance are less clear. Measures such as modularity or participation coefficient, which are theoretically important indices of the optimization of network function, did not show any relation to performance on different neuropsychological tests in young or older adults. In general, neuropsychological tests tend to be related to a wide range of underlying cognitive functions. These tests are not very specific to a particular domain. In contrast, the selective attention task that we used in chapters 5 and 7, measured very specific differences between individuals in cognitive functioning. When we related performance on these tests to individual differences in functional connectivity, we were able to detect clear links between connectivity and behavior. Therefore, it is possible that more specific measures of cognitive function are needed to increase our understanding of how connectivity changes impact behavior.

In addition, it might be necessary to use more specific measures of brain function. Modularity and local efficiency over the entire brain network are, for example, very global measures of brain functioning (chapter 3). Possibly, individual differences in such global measures do not relate directly to individual differences in behavior. Instead, it might be the case that individual differences in connections within or between specific functional networks have a much stronger link to cognitive functioning. The results in chapters 5

and 7, but also in chapter 3, support this idea. There we found clear relations between task performance and specific measures of connectivity between functional networks.

Another factor that might help to establish the link between brain function and behavior is the study of brain dynamics. Recent studies have shown that functional connectivity varies dynamically over time and that these dynamics could be an important dimension of brain function. Allen and colleagues (2012) have measured functional connectivity in brief time periods, using a sliding window approach. By clustering the different connectivity patterns observed, they were able to distinguish different sets of connectivity states. In some cases, these connectivity states were markedly different from the traditionally reported functional networks. This suggests that the functional networks that can be identified over long periods of time represent the most frequently occurring state of functional connectivity, but this does not necessarily mean that these are the only configurations used by the brain to transfer information. The functional connectivity patterns recorded over a period around the onset of a stimulus might have a clearer link to behavior at that time than the connectivity averaged over longer time periods. In addition, different researchers now suggest that the variability in brain activity and connectivity over time provide a window into the dynamic range of brain function (Deco et al., 2011; Garrett et al., 2013b; He, 2013).

In a series of papers Garrett and colleagues have demonstrated that this dynamic range of brain function might be reduced in older adults. They have shown that variability in the BOLD signal declines with age in a large number of brain regions (Garrett et al., 2010; Garrett et al., 2011; Garrett et al., 2013a). In addition, they showed that this variability has a clear functional significance, as it increases during task performance compared to resting state conditions (Garrett et al., 2013a) and it is related to more consistent and faster performance (Garrett et al., 2011). Strikingly, the task-related increases in variability are not limited to the task positive areas that generally show an increased mean signal during task performance compared to resting state. It is likely that the increased BOLD variability reflects a greater dynamic range of possible responses to incoming stimuli.

These new directions of research point to the importance of studying age-related changes in the spontaneous fluctuations in brain function. This is important, both because these spontaneous fluctuations have a clear relation to cognitive function and because the brain state at the time of stimulus onset determines the brain's response to that stimulus (He, 2013). Therefore, to truly understand how age-related differences in brain function relate to differences on the behavioral level, it is necessary to examine the (functional) nature of these spontaneous fluctuations in much more detail.

## 8.4 Conclusions

Aging equals change. In this thesis we observed that aging is associated with large-scale changes in connectivity within and between functional networks. Moreover, adaptation of functional connectivity to the demands of the task at hand proceeds differently in older compared to younger participants. Besides changes associated with age-related decline, we also found that there are specific adaptations in brain function that are associated with higher levels of selective attention in older adults. Further disentangling the passive age-related changes from active adaptation in brain function is an important challenge for future studies. Charting the limits of flexibility in the aging brain as well as understanding the factors that might trigger functional adaptations is important for the development of future interventions in healthy as well as pathological aging.

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## Korte samenvatting

Ouder worden we allemaal, toch is er nog veel onbekend over de oorzaken achter de veranderingen in cognitief functioneren die samengaan met veroudering. In dit proefschrift onderzoeken we hoe communicatie tussen hersengebieden verandert bij veroudering en hoe dit cognitief functioneren beïnvloedt. Er zijn groepen hersengebieden die meer met elkaar communiceren dan met andere hersengebieden, deze gebieden vormen samen een netwerk. Wij hebben laten zien dat deze hersennetwerken bij ouderen minder duidelijk van elkaar te onderscheiden zijn doordat functionele connectiviteit tussen netwerken toeneemt, terwijl de connectiviteit binnen specifieke netwerken afneemt in vergelijking met jongeren. Verder vonden we aanwijzingen dat deze afnemende communicatie in specifieke netwerken ook samengaat met slechter cognitief functioneren van ouderen. Eén specifieke cognitieve functie hebben we in meer detail onderzocht; selectieve aandacht. Selectieve aandacht is het mechanisme waarmee we aandacht kunnen besteden aan die dingen in de omgeving die voor ons belangrijk zijn en tegelijkertijd de onbelangrijke informatie uit de omgeving kunnen negeren. Dit tweede mechanisme is noodzakelijk omdat er op elk moment een grote hoeveelheid informatie via onze zintuigen binnenkomt die we niet allemaal kunnen verwerken. Voor ouderen wordt het met name lastiger om informatie te negeren die niet van belang is. Met ons onderzoek hebben we laten zien dat de hersenen, voordat informatie binnenkomt, zich kunnen voorbereiden op wat komen gaat en dat dit een belangrijke rol speelt bij het onderdrukken van irrelevante informatie. Bovendien vonden we dat ouderen tot op zekere hoogte de fysieke achteruitgang van hun hersenen kunnen compenseren bij het uitvoeren van de selectieve aandachtstaak door extra hersengebieden te activeren en de communicatie tussen specifieke hersengebieden te verhogen. De inzichten die dit soort fundamenteel onderzoek ons geeft, zijn belangrijk om nieuwe aanknopingspunten te geven voor het ontwikkelen van nieuwe interventies om het cognitief functioneren van ouderen langer op peil te houden.

Over deze resultaten, de methoden erachter en de betekenis ervan is meer informatie te vinden in de uitgebreide Nederlandse samenvatting.

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## Nederlandse samenvatting

Ouder worden we allemaal. Op een bepaald moment zullen de meeste mensen weten wat het is om oud te worden. Veroudering is een proces van verandering. Veroudering is namelijk niet alleen het resultaat van passieve achteruitgang met de tijd, maar het is een proces waarin door een voortdurende wisselwerking tussen toegenomen ervaring en kennis en de fysieke veranderingen die gepaard gaan met veroudering nog van alles mogelijk is.

Ouder worden gaat gepaard met positieve, maar ook met negatieve veranderingen. Ouderen zijn vaak beter in staat om te gaan met hun emoties dan jongeren en door hun levenservaring kunnen ze beter omgaan met sociale conflicten. Aan de andere kant gaan sommige cognitieve functies achteruit bij veroudering; ouderen ervaren bijvoorbeeld vaak dat ze minder goed dingen kunnen onthouden dan vroeger. Bovendien reageren ouderen langzamer op gebeurtenissen in de omgeving en zijn ze sneller afgeleid dan jongeren. Maar dit geldt niet voor alle ouderen in gelijke mate: er zijn grote verschillen tussen mensen in de effecten van het ouder worden. De een merkt een snelle achteruitgang in de cognitieve functies terwijl bij de ander nauwelijks achteruitgang te merken is. In dit proefschrift proberen we te achterhalen wat de oorzaken zijn van deze verschillen tussen mensen. Dit doen we door te kijken naar de hersenmechanismen die ten grondslag liggen aan de verschillen tussen ouderen in cognitief functioneren.

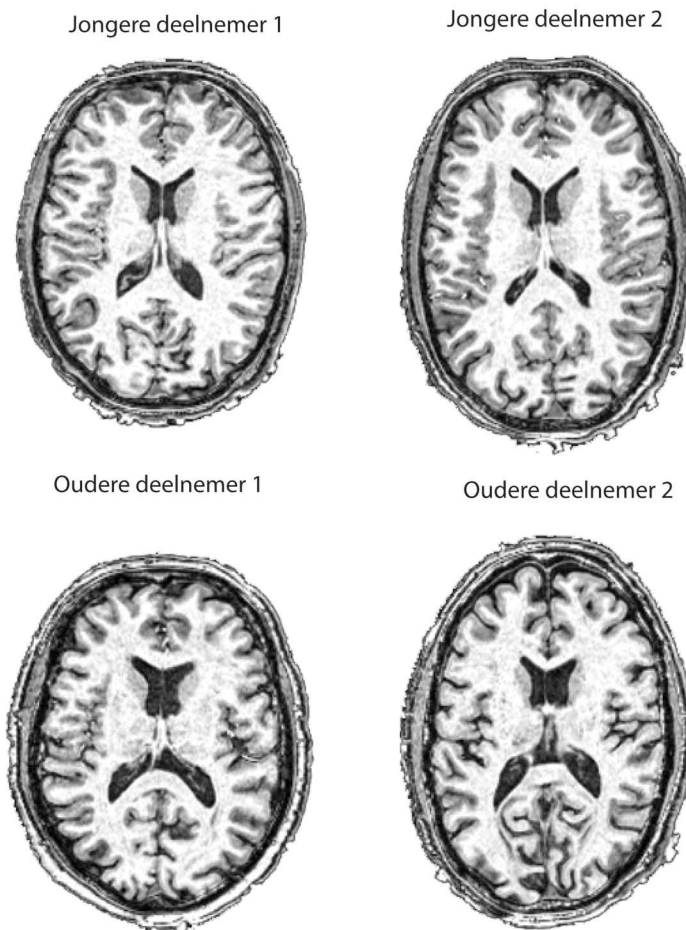
### Een belangrijke cognitieve functie: selectieve aandacht

Eén van de cognitieve functies die met name van belang is voor goed functioneren in het dagelijks leven is "selectieve aandacht". Selectieve aandacht is het mechanisme waarmee we aandacht kunnen besteden aan die dingen in de omgeving die voor ons belangrijk zijn en tegelijkertijd de onbelangrijke informatie uit de omgeving kunnen negeren. Dit tweede mechanisme is noodzakelijk omdat er op elk moment een grote hoeveelheid informatie via onze zintuigen binnenkomt die we niet allemaal kunnen verwerken. Voor wie vertrouwd is met computers; er is geschat dat er elke seconde ongeveer 10 miljoen bits aan informatie via je ogen binnenkomt. Dat is evenveel informatie als op ruim 500 van deze proefschrift pagina's staat. Het is dus erg belangrijk dat met behulp van selectieve aandacht de juiste informatie hieruit gefilterd wordt. Stel je maar eens voor dat je op een feestje bent. De kamer is vol met mensen die allemaal druk door elkaar heen praten. Jij hebt midden in die kamer een leuk gesprek aan het voeren met je beste vriend. Op dat moment ben je, als het goed is, in staat om alle gesprekken die in de kamer om je heen gevoerd worden te negeren en je te richten op het gesprek met je vriend. Waarschijnlijk heb je ook wel eens meegemaakt dat je moe was op een feestje en dat het ineens een stuk moeilijker was om al die gesprekken om je heen te negeren; je wordt dan sterker afgeleid. Het voeren van een goed gesprek met je vriend is dan ook ineens een stuk lastiger. Bij het

ouder worden gaan selectieve aandacht mechanismen achteruit. Met name het negeren van informatie die niet van belang is, lijkt minder goed te gaan.

## Effecten van veroudering op de hersenen

In dit proefschrift onderzoeken we de mechanismen die ten grondslag liggen aan de veranderingen in het cognitief functioneren met veroudering. Hierbij kijken we vanuit het perspectief van de hersenen. Met het ouder worden veranderen er veel dingen in de hersenen die een direct effect hebben op het functioneren van ouderen. Zo sterven er bijvoorbeeld zenuwcellen (grijze stof) af, met name in het voorste deel, de frontale kwab, van de hersenen (zie figuur 1).



Figuur 1: Een dwarsdoorsnede van de hersenen van vier van de deelnemers aan ons onderzoek. De bovenste twee zijn jongere deelnemers, de onderste twee oudere deelnemers. Opvallend is dat de ventrikels (zwarte gaten in het midden) groter worden bij ouderen. Bovendien is er meer ruimte tussen de windingen van de hersenen die aan de zijkant zichtbaar zijn. Dit wijst op een afname in grijze en witte stof bij de oudere deelnemers. Natuurlijk hebben niet alle verschillen te maken met veroudering, tussen mensen zijn er ook grote verschillen in de structuur van de hersenen.



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Ook de witte stof, waarin de verbindingen liggen tussen zenuwcellen, wordt aangetast door veroudering. Toch kunnen deze veranderingen in de structuur (of de hardware) van de hersenen niet volledig de achteruitgang in het functioneren van ouderen verklaren. Dit komt omdat de hersenen zich tot op zekere hoogte kunnen aanpassen aan de veranderingen in de structuur. Onderzoek heeft bijvoorbeeld laten zien dat bij ouderen vaak meer hersengebieden ingezet worden tijdens het uitvoeren van een taak dan bij jongeren. Dit is door verschillende onderzoekers aangevoerd als bewijs voor 'compensatie-mechanismen'. Het idee is dat de hersenen van ouderen hun prestaties op een taak op peil kunnen houden, ondanks de achteruitgang in grijze en witte stof, door extra hersengebieden in te zetten om de taak goed uit te voeren. Er zijn echter ook andere onderzoeken die laten zien dat de inzet van extra hersengebieden juist een aanwijzing voor achteruitgang zou kunnen zijn. Deze onderzoekers zeggen dat de extra activiteit in de hersenen een teken is dat de oudere hersenen niet meer goed kunnen bepalen welke hersengebieden ingezet moeten worden bij een taak.

Samengevat zijn er dus aanwijzingen dat zowel de structurele veranderingen in de hersenen als de veranderingen in functie van bepaalde hersengebieden een rol spelen bij de veranderingen ten gevolge van veroudering. De resultaten tot zover zijn echter niet consistent en kunnen niet volledig de veranderingen in cognitieve functies verklaren die gepaard gaan met het ouder worden. Dit komt ook omdat een belangrijk aspect van hersenfunctie tot nu toe weinig aandacht heeft gekregen in het onderzoek naar veroudering. Dat is de informatie-uitwisseling tussen verschillende hersengebieden. Tussen het moment waarop informatie binnenkomt in de hersenen en het moment waarop gereageerd wordt zitten veel verwerkingsstappen. Er zijn gebieden in onze hersenen die de binnenkomende visuele informatie ontcijferen en ons in staat stellen om objecten te herkennen, gebieden die in de gaten houden wat de doelen zijn van de taak waar we mee bezig zijn en er zijn gebieden die op basis van de verzamelde informatie beslissen welke reactie gegeven moet worden. Om dit goed te laten verlopen is het essentieel dat alle hersengebieden, die elk voor een deel van de verwerkingsstappen verantwoordelijk zijn, op de juiste manier en op het juiste moment met elkaar communiceren. Er is echter niet veel bekend over de manier waarop deze informatie-uitwisseling wordt beïnvloed door het verouderingsproces. Een van de belangrijke doelen van dit proefschrift is om te laten zien hoe de informatie-uitwisseling tussen hersengebieden verandert met veroudering en of dit het cognitief functioneren van ouderen beïnvloedt.

## Het meten van hersenactiviteit

De mate waarin bepaalde hersengebieden actief worden en de mate waarin hersengebieden informatie met elkaar uitwisselen kan onderzocht worden met verschillende technieken. In dit proefschrift is gebruik gemaakt van elektro-encefalografie (EEG) en functionele magnetische resonantie imaging (fMRI, zie figuur 2). Tijdens een EEG

meting wordt er een “badmuts” op het hoofd van de deelnemer gezet waarin elektroden zijn bevestigd. Deze elektroden kunnen de elektrische activiteit van de hersenen meten. Tijdens een EEG registratie wordt elke milliseconde de hersenactiviteit gemeten en kan gekeken worden hoe deze activiteit verandert als iemand een bepaalde taak uitvoert. Het nadeel van het EEG is dat we niet heel nauwkeurig kunnen bepalen waar in de hersenen de activiteit precies vandaan komt.



Figuur 2: hersenmetingen met EEG (links) en fMRI (rechts)

Deze locatie kunnen we wel goed bepalen met behulp van de fMRI techniek. Deze techniek maakt gebruik van een sterk magnetisch veld om de verandering in hersenactiviteit te meten als iemand een taak uitvoert. Als een gebied in de hersenen betrokken is bij het uitvoeren van een taak, dan gebruikt het gebied meer zuurstof. Als reactie hierop wordt door de bloedvaten meer zuurstofrijk bloed aangevoerd. Dit zorgt voor een verandering in de verhouding tussen zuurstofarm en zuurstofrijk bloed ter plaatse en deze verandering kunnen we meten doordat zuurstofrijk en zuurstofarm bloed anders reageren op het magnetische veld. Zo kunnen we onderzoeken waar in de hersenen de activiteit toeneemt als iemand een taak uitvoert. Met fMRI is het mogelijk om tot op een aantal millimeters nauwkeurig te bepalen welk hersengebied actief is tijdens het uitvoeren van cognitieve taken. EEG is daarentegen juist erg goed in het bepalen wanneer de activiteit in een gebied verandert. In de onderzoeken beschreven in dit proefschrift gebruiken we zowel EEG als fMRI omdat de technieken elkaar goed aanvullen.

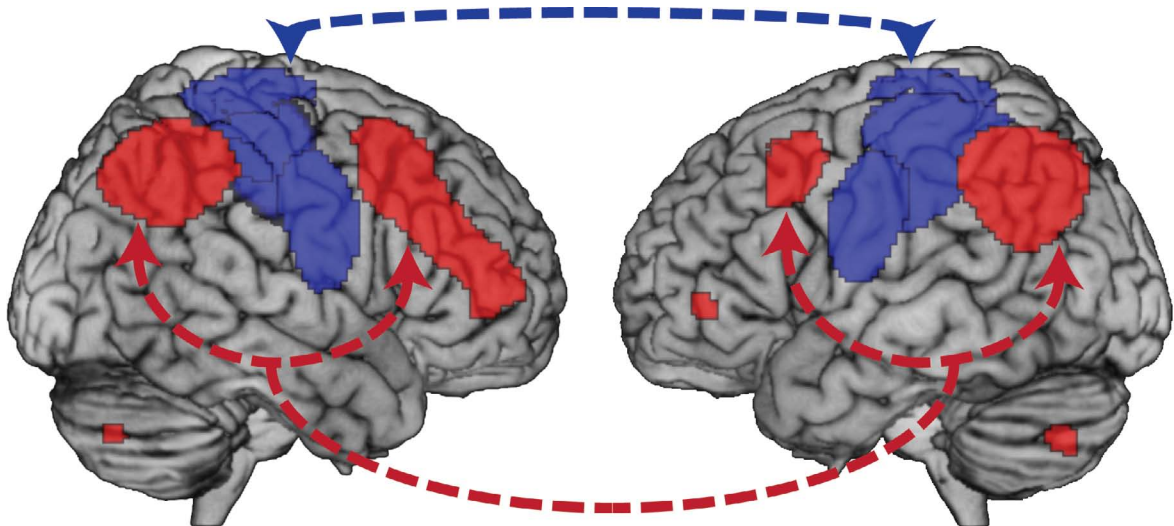
Naast het bepalen van waar en wanneer de activiteit in bepaalde hersengebieden verandert, kunnen EEG en fMRI ook gebruikt worden om de informatie-uitwisseling tussen gebieden in kaart te brengen. Als de activiteit in twee gebieden gedurende langere tijd met elkaar mee varieert kunnen we constateren dat er communicatie tussen deze gebieden is. Deze informatie-uitwisseling tussen gebieden noemen we functionele connectiviteit.

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## Informatie-uitwisseling in de oudere hersenen

In het eerste deel van dit proefschrift onderzoeken we wat de invloed is van veroudering op de functionele connectiviteit in de hersenen. Communicatie tussen hersengebieden wordt veroorzaakt doordat grote groepen zenuwcellen tegelijkertijd in hetzelfde ritme (met dezelfde frequentie) gaan vuren. Ongeveer 12 jaar geleden werd voor het eerst ontdekt dat er groepen van hersengebieden zijn, die meer met elkaar communiceren dan met andere gebieden. Deze groepen gebieden communiceren met elkaar wanneer mensen een taak uitvoeren, wanneer ze rustig met hun ogen dicht in de scanner liggen en zelfs wanneer ze slapen. Deze groepen van gebieden worden hersennetwerken genoemd. De verschillende gebieden in zo'n hersennetwerk worden vaak samen actief tijdens het uitvoeren van specifieke cognitieve functies. Het eerste netwerk dat ontdekt werd is het 'default mode netwerk' (standaard-modus netwerk). Dit netwerk heeft zijn naam gekregen omdat de gebieden in het netwerk het meest actief zijn wanneer een deelnemer in rust is, en niet gericht is op gebeurtenissen in de buitenwereld. Een tweede belangrijk hersennetwerk is het somato-motorische netwerk (zie figuur 3). Dit is een netwerk dat een belangrijke rol speelt bij taken die een beroep doen op de tastzin en het plannen en uitvoeren van bewegingen. Er zijn ook netwerken die zich bezig houden met het coördineren van de informatieverwerking in andere netwerken, de zogenaamde regel- of coördinatie-netwerken. Zo speelt het dorsale aandachtsnetwerk een belangrijke rol bij selectieve aandacht; het richten van aandacht op belangrijke informatie en het onderdrukken van onbelangrijke informatie die binnenkomt. Een ander coördinerend netwerk is het fronto-pariëtale controle netwerk (zie figuur 3), dit netwerk zorgt ervoor dat we de doelen in de gaten houden van de taak waar we mee bezig zijn en stelt ons in staat om strategieën te bepalen, beslissingen te maken en plannen te maken voor de toekomst.

Onderzoek heeft laten zien dat de functionele connectiviteit (de communicatie) in het default mode netwerk achteruit gaat als mensen ouder worden. Bovendien is gevonden dat deze achteruitgang gerelateerd is aan een minder goed functionerend geheugen en een tragere reactiesnelheid. Dit onderzoek gaf een eerste indicatie dat er veranderingen zijn in de functionele connectiviteit bij het ouder worden en dat deze veranderingen het functioneren van ouderen beïnvloeden. In dit proefschrift hebben we die veranderingen onder de loep genomen. We hebben niet alleen gekeken hoe de functionele connectiviteit binnen netwerken verandert als mensen ouder worden, maar ook hoe functionele connectiviteit tussen verschillende netwerken wordt beïnvloed door veroudering. Bij jonge volwassenen vindt voornamelijk veel communicatie plaats tussen gebieden die tot één bepaald netwerk behoren.



Figuur 3: Zijaanzicht van de rechter en linkerkant van een model van het menselijk brein; twee verschillende hersennetwerken zijn in kleur aan gegeven. In rood het fronto-pariëtale controle netwerk en in blauw het somato-motorische netwerk.

Gebieden die bij verschillende netwerken horen communiceren onderling veel minder met elkaar. In hoofdstuk 2, laten we zien dat het onderscheid tussen verschillende netwerken in de hersenen minder sterk wordt bij veroudering. Dit komt doordat de verbindingen binnen de netwerken afnemen; vooral binnen het default mode netwerk en somato-motorische netwerk. Tegelijkertijd nemen verbindingen tussen de verschillende netwerken toe.

De studie in hoofdstuk 2 gaf ons een eerste indicatie dat er inderdaad veranderingen in de hersennetwerken optreden wanneer mensen ouder worden. In hoofdstuk 3 hebben we deze veranderingen in meer detail onderzocht. Hiervoor hebben we een nieuwe techniek gebruikt om naar de hersennetwerken te kijken. Deze techniek heet grafentheorie, en wordt bijvoorbeeld ook gebruikt in het bestuderen van de dynamiek in sociale netwerken. Met deze techniek kunnen we mensen in een sociaal netwerk bekijken als knopen. Vriendschappen of familiebanden vormen de verbindingen tussen die knopen. Wanneer we op die manier een sociaal netwerk beschrijven kunnen we vervolgens kijken hoe de informatie in zo'n netwerk verspreid wordt. Bijvoorbeeld: stel dat informatie bij één persoon in het netwerk aanwezig is; hoe snel kan de informatie dan verspreid worden naar andere personen in dat netwerk? Of in andere woorden, als één van je vrienden een nieuwtje heeft over jou, hoe lang duurt het dan voordat al je vrienden dit weten? Dit wordt de globale efficiëntie van het netwerk genoemd. Een ander voorbeeld: als één van de personen uit het netwerk weg zou vallen, zouden de vrienden van deze personen dan nog met elkaar 'verbonden zijn'? Dus, als een vriendin ineens naar Engeland verhuist, heb je dan nog contact met de vrienden van die vriendin? Dit is de lokale efficiëntie van een knoop in het netwerk.

Deze methode kunnen we ook toepassen op de hersenen. We beschouwen dan een hersengebied als een knoop in het netwerk en de functionele connectiviteit tussen

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hersengebieden als de verbindingen tussen die knopen. In hoofdstuk 3 hebben we op deze manier het functioneren van hersennetwerken van jongere en oudere deelnemers met elkaar vergeleken. We vonden dat de verspreiding van informatie in het gehele netwerk (globale efficiëntie) niet veranderde met leeftijd. Er waren in specifieke netwerken echter minder verbindingen tussen verschillende knopen in het netwerk (de lokale efficiëntie ging omlaag). Dit was vooral zo voor netwerken die betrokken waren bij coördinerende functies (het cingulo-operculaire netwerk en het fronto-pariëtale controle netwerk) en voor het default mode netwerk. De effecten van veroudering zijn dus niet in alle netwerken even sterk. Daarnaast vonden we in hoofdstuk 3 ook dat functionele connectiviteit tussen netwerken toe nam in ouderen. De resultaten die we hebben gevonden met deze grafentechniek bevestigden de eerdere bevindingen die beschreven zijn in hoofdstuk 2. We vonden opnieuw dat er meer verbindingen waren tussen verschillende hersennetwerken in ouderen (in het bijzonder tussen het somatomotorische en het visuele netwerk) dan in jongeren. Samen gevat zijn hersennetwerken bij ouderen minder van elkaar onderscheiden doordat functionele connectiviteit tussen netwerken toeneemt terwijl de connectiviteit binnen specifieke netwerken afneemt in vergelijking met jongeren.

Verder hebben we in hoofdstuk 3 geprobeerd om beter in kaart te brengen hoe deze veranderingen samenhangen met veranderingen in cognitieve functies bij ouderen. Dit hebben we gedaan door de individuele verschillen in netwerkeigenschappen te relateren aan de individuele verschillen in prestatie op verschillende testen voor bijvoorbeeld reactiesnelheid en geheugen. We vonden dat minder communicatie tussen de gebieden in het default mode netwerk en in het controle netwerk gepaard ging met slechtere prestatie op verschillende testen. De afgenomen connectiviteit in speciaal deze netwerken bij ouderen lijkt dus wel een teken van achteruitgang te zijn.

De functionele connectiviteit tussen specifieke gebieden die tot een bepaald netwerk horen en tussen verschillende netwerken is afhankelijk van de taak waar iemand mee bezig is. Gebieden die belangrijk zijn voor een bepaalde taak gaan meer met elkaar samenwerken als iemand die taak uitvoert. Zonder deze flexibiliteit zou je een specifieke taak niet goed kunnen uitvoeren. In hoofdstuk 4 hebben we daarom onderzocht in welke mate ouderen nog in staat zijn functionele connectiviteit flexibel aan te passen aan de taak waar ze mee bezig zijn. We hebben de hersenactiviteit en het gedrag van oudere en jongere deelnemers gemeten (1) terwijl ze een geheugentaak deden, (2) terwijl ze een aandachtstaak deden en (3) tijdens rust. Bovendien hebben we taakmoeilijkheid gevarieerd in de geheugentaak door mensen meer te laten onthouden. Vervolgens hebben we gekeken hoe de functionele connectiviteit af hing van de taak die de proefpersoon uitvoerde. Hierbij hebben we vooral gelet op de connectiviteit tussen verschillende netwerken. De resultaten lieten zien dat ouderen nog steeds flexibel connectiviteit kunnen aanpassen aan de taak waar ze mee bezig zijn. Opvallend was echter dat ouderen veel grotere veranderingen in connectiviteit lieten zien dan jongeren bij het uitvoeren



van een simpele taak ten opzichte van rust. Aan de andere kant waren er bij ouderen minder verschillen in netwerkeigenschappen dan bij jongeren als we de simpele taak vergeleken met een moeilijkere taak. Dit zou erop kunnen wijzen dat ouderen relatief meer inspanning moeten leveren als ze een simpele taak uitvoeren ten opzichte van rust, dan jongeren. Doordat ze tijdens simpele taken al relatief veel energie investeren is het vervolgens lastig om deze inspanning nog verder te verhogen wanneer de taak moeilijker wordt. Wanneer het plafond is bereikt, en ouderen niet meer inspanning kunnen leveren dan ze al doen, zien we dat de prestatie op de taak achteruit gaat. Ouderen kunnen zich dan niet meer aanpassen aan de eisen die de taak aan hen stelt. Bij jongeren wordt het plafond minder snel bereikt.

## Selectieve aandacht in de oudere hersenen

In het eerste deel van dit proefschrift (hoofdstukken 2, 3 en 4) hebben we gekeken naar algemene veranderingen in de communicatie tussen hersengebieden door functionele connectiviteit te onderzoeken. In het tweede deel van dit proefschrift (hoofdstukken 5-7) hebben we vervolgens onderzocht welke hersenmechanismen een rol spelen in de leeftijd gerelateerde veranderingen in selectieve aandacht en welke rol de veranderingen in connectiviteit hierin spelen. We wisten al dat het richten van aandacht op relevante informatie en het negeren van onbelangrijke informatie in de hersenen worden geregeld door een aantal verschillende hersengebieden. Vooral vanuit gebieden in het dorsale aandachtsnetwerk wordt een sterke invloed uitgeoefend op hersengebieden die betrokken zijn bij de verwerking van de informatie die binnen komt, via bijvoorbeeld het gehoor of de ogen. Het dorsale aandachtsnetwerk zorgt er vervolgens voor dat de informatie die belangrijk is voorrang krijgt, terwijl de verwerking van onbelangrijke informatie wordt onderdrukt. Om dat voor elkaar te krijgen is het belangrijk dat de betrokken hersengebieden samenwerken en informatie met elkaar uitwisselen. In hoofdstukken 5 en 7 hebben we onderzocht hoe deze informatie uitwisseling door veroudering wordt beïnvloed. In dit onderzoek voerden de oudere en jongere deelnemers een selectieve aandachtstaak uit waarin belangrijke en onbelangrijke informatie tegelijkertijd op een scherm kon verschijnen. Hiermee konden we bepalen in hoeverre mensen werden afgeleid door onbelangrijke informatie. We vonden dat gemiddeld genomen de oudere mensen inderdaad meer werd afgeleid door de onbelangrijke informatie dan de jongere mensen. Maar belangrijk is, is dat niet alle ouderen deze achteruitgang lieten zien.

We hebben vervolgens onderzocht of verschillen in connectiviteit deze verschillen tussen mensen zou kunnen verklaren. Terwijl we in hoofdstukken 2, 3 en 4 met behulp van fMRI metingen naar connectiviteit gekeken hebben, hebben we dat in hoofdstuk 5 met behulp van EEG metingen onderzocht. Hersengebieden communiceren op verschillende frequenties, een beetje vergelijkbaar met radiosignalen die op verschillende golflengtes worden uitgezonden. Met behulp van EEG kunnen we naar communicatie op al deze

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verschillende frequenties kijken. De rol van deze communicatie hangt af van de specifieke frequentieband waar binnen de communicatie plaats vindt. Communicatie in de zogenaamde alfa frequentieband speelt bijvoorbeeld vooral een rol bij het onderdrukken van informatieverwerking. Dit onderdrukken van informatieverwerking is belangrijk om te voorkomen dat iemand wordt afgeleid door onbelangrijke informatie in de omgeving. Door de connectiviteit binnen de alfa frequentieband te onderzoeken, hebben we in hoofdstuk 5 laten zien dat de verschillen tussen mensen in de mate waarin ze afgeleid werden door onbelangrijke informatie inderdaad voor een deel veroorzaakt werden door verschillen in de samenwerking tussen hersengebieden. Wanneer er meer communicatie was in de alfa band tussen de frontale (coördinerende) gebieden en de gebieden die de visuele informatie verwerken, waren deelnemers beter in staat onbelangrijke informatie te negeren. Belangrijk was dat deze toegenomen communicatie plaatsvond vlak voor de informatie op het scherm verscheen. Hieruit kunnen we concluderen dat de deelnemers zich voorbereiden op de taak die ging komen door de communicatie tussen de frontale en visuele gebieden te optimaliseren. Deze resultaten vertellen ons ook dat de hersenen, voordat informatie binnenkomt, voorbereid kunnen worden op wat komen gaat en dat dit een belangrijke rol speelt bij de daarop volgende informatie verwerking.

In hoofdstuk 6 hebben we verder onderzocht hoe de toestand van de hersenen, voordat informatie binnenkomt, bepaalt hoe deze informatie wordt verwerkt. In deze studie kregen mensen 2 keer heel snel achter elkaar een afbeelding van elk 12 vierkantjes te zien. In ongeveer de helft van de gevallen dat deze afbeeldingen getoond werden aan de deelnemers, zagen ze twee aparte afbeeldingen. Maar in de andere helft van de gevallen hadden mensen de indruk dat ze maar één samengevoegde afbeelding van 24 vierkantjes zagen. Dit laatste verschijnsel wordt temporele integratie genoemd. In deze studie hebben we gekeken wat er in de hersenen gebeurt zodat mensen soms twee afbeeldingen zien en soms maar één. We vonden dat mensen vaak één afbeelding zagen in plaats van twee, wanneer het brein al voor het verschijnen van de afbeeldingen meer actief was in de beta frequentie band. De beta frequentieband is een andere frequentieband in het EEG, die met name belangrijk is bij richten van aandacht op belangrijke dingen in de omgeving. De toestand van de hersenen, al voordat de plaatjes verschijnen, lijkt dus te bepalen hoe we informatie waarnemen. Dit resultaat geeft aan dat het erg belangrijk is om niet alleen te kijken hoe de hersenen reageren als we iets hebben laten zien, maar ook te kijken naar de toestand van de hersenen voordat de deelnemers informatie te zien krijgen.

In hoofdstuk 5 vonden we ook aanwijzingen dat ouderen tot op zekere hoogte de fysieke achteruitgang van hun hersenen kunnen compenseren bij het uitvoeren van de selectieve aandachtstaak. Ouderen die meer connectiviteit lieten zien tussen frontale en visuele gebieden in de beta frequentieband, waren namelijk ook beter in staat om onbelangrijke informatie te negeren. Bij de jongere deelnemers speelde connectiviteit in de beta frequentieband helemaal geen rol bij het onderdrukken van onbelangrijke informatie. Ook in hoofdstuk 7 vonden we aanwijzingen dat ouderen door het activeren



van extra hersengebieden ervoor kunnen zorgen dat hun prestatie op peil blijft. In die studie hebben we met behulp van fMRI de hersenactiviteit van deelnemers onderzocht tijdens het uitvoeren van de selectieve aandachtstaak. In deze studie keken we vooral naar de verschillen in hersenactiviteit en gedrag tussen ouderen en jongeren tijdens het detecteren van en reageren op een bepaalde letter die mensen in hun geheugen moesten opslaan voordat de taak begon. We vonden dat jongeren tijdens taakuitvoering vooral het somato-motorische netwerk activeren. Ouderen gebruikten daarnaast ook het fronto-pariëtale controle netwerk tijdens de uitvoering van deze cognitieve taak. Het lijkt er op dat het fronto-pariëtale netwerk bij ouderen meer betrokken is bij de aansturing van de respons die gegenereerd werd in het somato-motorische netwerk. Dit bleek ook uit de verhoogde connectiviteit tussen het somato-motorische netwerk en het fronto-pariëtale controle netwerk bij ouderen. Bovendien was deze toegenomen connectiviteit bij ouderen gerelateerd aan een betere prestatie op de taak. Ook in dit geval zetten de ouderen blijkbaar extra hersenen gebieden in om hun prestatie op peil te houden; ze compenseren blijkbaar op die manier voor de fysieke achteruitgang van de hersenen.

## Conclusies

In dit proefschrift hebben we laten zien dat de communicatie tussen hersengebieden verandert als mensen ouder worden. De verbindingen binnen netwerken nemen af ten gevolge van veroudering terwijl de verbindingen tussen netwerken toenemen. Hierdoor zijn bij ouderen de afzonderlijke hersennetwerken minder goed te onderscheiden. Bovendien hebben we laten zien dat de afname in connectiviteit binnen verschillende netwerken een negatief effect heeft op het functioneren van ouderen. Aan de andere kant hebben we ook laten zien dat functionele connectiviteit van groot belang is voor het efficiënt richten van aandacht. Door connectiviteit tussen bepaalde hersenen gebieden te verhogen waren de ouderen in staat om, tot op zekere hoogte, te compenseren voor de fysieke achteruitgang van hun hersenen. Veranderingen in connectiviteit kunnen dus zowel positieve als negatieve effecten hebben op het cognitief functioneren van ouderen.

Omdat de effecten van veroudering het dagelijks leven van ons allemaal beïnvloeden is het belangrijk dat we onderzoek blijven doen naar wat er precies gebeurt in de hersenen als mensen ouder worden en hoe dit proces het functioneren van ouderen bepaalt. In de toekomst kunnen we deze informatie misschien gebruiken om trainingsmethoden voor ouderen te ontwikkelen die er voor zouden kunnen zorgen dat ouderen zo lang mogelijk mentaal goed kunnen blijven functioneren.

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## Begrippen lijst

**Selectieve aandacht** Het mechanisme waardoor we in staat zijn om onze aandacht te richten op belangrijke informatie in de omgeving en onbelangrijke informatie te negeren.

**Compensatie** De inzet van extra hersengebieden of verbindingen tussen verschillende hersengebieden, waardoor de prestatie van ouderen op peil blijft ondanks fysieke achteruitgang van de hersenen.

**Cognitieve functies** Verschillende processen die betrokken zijn bij het opnemen, het verwerken en het reageren op informatie, zoals bijvoorbeeld geheugen en aandacht.

**fMRI** De meting van hersenactiviteit met behulp van sterke magnetische velden. Met fMRI kan heel precies bepaald worden waar hersenactiviteit verandert. Doordat fMRI slechts elke 2 seconden een nieuwe meting doet kan minder goed bepaald worden wanneer hersenactiviteit verandert.

**EEG** De meting van elektrische activiteit in de hersenen met behulp van elektroden die bevestigd zijn in een soort badmuts. Met EEG kan heel specifiek gekeken worden wanneer hersenactiviteit verandert. EEG is minder goed in het in kaart brengen van waar hersenactiviteit plaats vindt.

**Hersennetwerk** Een groep hersengebieden die sterk met elkaar communiceren en minder met gebieden die horen bij andere netwerken.

**Default mode netwerk** Een netwerk dat het meest actief is wanneer we in rust zijn en niet gericht zijn op gebeurtenissen in de buitenwereld.

**Dorsale aandachtsnetwerk** Een netwerk dat een belangrijke rol speelt bij aandacht; het richten van aandacht op belangrijke informatie en het onderdrukken van onbelangrijke informatie die binnenkomt.

**Fronto-pariëtale controle netwerk** Een netwerk dat ervoor zorgt dat we de doelen in de gaten houden van de taak waar we mee bezig zijn. Dit netwerk stelt ons ook in staat om strategieën te bepalen, beslissingen te nemen en plannen te maken voor de toekomst.

**Somato-motorische netwerk** Een netwerk dat betrokken is bij het plannen en aansturen van bewegingen en de tastzin.

**Visuele netwerk** Het netwerk dat een rol speelt bij de verwerking van informatie die via de ogen binnenkomt, belangrijk voor de visuele waarneming.

**Frequentieband** Hersengebieden communiceren op verschillende frequenties. Met behulp van EEG kunnen we naar communicatie op al deze verschillende frequenties kijken. Frequenties die dicht bij elkaar liggen worden vaak samen beschreven als een frequentieband. De rol van deze communicatie hangt af van de specifieke frequentieband waar binnen de communicatie plaats vindt.

**Alfa band** De frequentieband die met name een rol speelt bij het onderdrukken van informatieverwerking in bepaalde hersengebieden. Dit is met name belangrijk bij het negeren van onbelangrijke informatie in de omgeving.

**Beta band** De frequentieband die met name een rol speelt bij het richten van aandacht op bepaalde informatie. Dit is met name belangrijk bij het verwerken van de informatie uit de omgeving die van belang voor het uitvoeren van een bepaalde taak.

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## Publication list

### Publications

Geerligs,L., Saliassi,E., Renken, R.J., Maurits,N.M., Lorist,M.M. (in press) Flexible connectivity in the aging brain revealed by task modulations. *Human Brain Mapping*

Geerligs,L., Maurits,M.M., Renken,R.J., Lorist,M.M. (2012). Reduced specificity of functional connectivity in the aging brain during task performance. *Human Brain Mapping* doi: 10.1002/hbm.22175

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Saliassi,E., Geerligs,L., Lorist,M.M., Maurits,N.M. (2013) The Relationship between P3 Amplitude and Working Memory Performance Differs in Young and Older Adults. *Plos One*, 8(5): e63701

### Submitted manuscripts

Geerligs,L., Renken, R.J., Saliassi,E., Maurits,N.M., Lorist,M.M. A brain wide study of age-related changes in functional connectivity.

Geerligs,L., Saliassi,E., Maurits,N.M., Renken, R.J., Lorist,M.M. Brain mechanisms underlying the effects of aging on different aspects of selective attention.

Saliassi,E., Geerligs,L., Lorist,M.M., Maurits,N.M. Neural correlates associated with successful working memory performance in older adults as revealed by spatial ICA.

Saliassi,E., Geerligts,L., Dalenberg, J., Lorist,M.M., Maurits,N.M. Profiling cognitive ageing: performance patterns revealed by community structure detection in younger and older adults.

Banis, H.M., Geerligts, L., Lorist,M.M. The effects of acute stress on oscillatory activity during feedback processing in men and women.

### Manuscripts in preparation

Servaas, M.N., Geerligts, L, Renken, R.J., Marsman, J.B.C., Ormel, J., Riese, H., Aleman, A. Disrupted functional network organization in individuals scoring higher on neuroticism.

Saliassi, E., Geerligts, L., Renken, R.J., Lorist,M.M., Maurits, N.M. Age- and load-dependent variability in the shared EEG – fMRI relationship.

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Aging equals change. Changes in brain function as well as in cognitive functioning. In this thesis I have attempted to link these two aspects of change. How do the changes in brain function produce changes in behavior? Why is it that older adults are distracted by irrelevant information more than younger adults? How does the communication between brain areas change with age and how does this impact functioning of older adults? Studies on these and other questions are presented in this thesis.

