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Abstract

Age-associated cognitive decline is particularly pronounced in executive functions such as interference control – the ability to suppress the processing of irrelevant information and to attend to a certain target stimulus. These deficits are also evident in patients that exhibit a pathological decline of cognition, as found in amnestic Mild Cognitive Impairment (aMCI), a preclinical phase of Alzheimer's dementia. Importantly, deficits of interference control can impede the performance of other cognitive domains and thus contribute to memory dysfunction in elderly with and without aMCI. In recent years, various studies have demonstrated that interference control consists of distinct subcomponents that are associated with different conflict tasks such as the Flanker conflict and the stimulus-response-conflict (SRC) task. Moreover, these subcomponents rely on distinct neural networks and exhibit specific temporal characteristics of neural processing. The present thesis investigates the effects of healthy and pathological ageing on different components of interference control. A combined Flanker and SRC task was conducted by young adults, healthy elderly and elderly with aMCI during electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI) recording. Experiment 1 focuses on the data of 20 young and 19 healthy elderly data obtained in the fMRI session. The analysis of the reaction time (RT) data indicates that the SRC effect is increased in healthy elderly, while the Flanker conflict effect is not altered in advanced age. Furthermore, the SRC elicits substantially different activation patterns in both groups. While elderly exhibited increased activation of parietal and prefrontal areas, young adults mainly showed a deactivation patterns in response to incongruent SRC trials. In contrast, the Flanker conflict was associated with activation of similar regions in both groups including caudate nucleus, middle occipital gyrus and cingulate gyrus with additional recruitment of the parietal and prefrontal areas in elderly. These data indicate that ageing differentially affects the processing of different conflict types. Experiment 2 included the data of 23 healthy elderly and 19 young controls. Behavioral data analysis revealed an increased SRC related RT effect in elderly in trials with rather slow responses. The analysis of the event-related potentials P2, N2 and P3 demonstrated that only elderly exhibited an increased P2 amplitude in response to the SRC. Moreover, the Flanker conflict enhanced the N2 amplitude in both groups, however, this modulation was stronger in young adults. The P3 amplitude was reduced by both conflict types. This reduction was more pronounced in healthy elderly. These data illustrate, that ageing effects on early processing stages reflected by the P2 and N2 component, are specific for the Flanker and the SRC task. In contrast, age-related differences of the P3 amplitude modulation are equivalent for both conflict types. The fMRI and the ERP data corroborate the assumption

that ageing has differential effects on the neural correlates associated with SRC and Flanker conflict processing. Furthermore, early processing stages seem to be particularly critical for the specificity of ageing effects.

Experiment 3 focuses on the comparison of 11 male elderly with aMCI and 11 healthy male controls with regard to ERP and fMRI data. There were no differences of RT and error rates between both groups. However, fMRI analysis revealed decreased activation of prefrontal and parietal regions of the left hemisphere in incongruent SRC trials in elderly with aMCI. Furthermore, in contrast to healthy controls aMCI participants showed no modulation of the P2 amplitude in response to the SRC.

In conclusion, the present results indicate that the additional neural recruitment and the increased modulation of neural correlates associated with healthy ageing represent compensatory mechanisms. The deterioration of this effect in elderly with aMCI points to a decompensation in pathological ageing. Furthermore, the effects of healthy and pathological ageing on interference control are specific for different subcomponents, whereas SRC-related processing seems to be particularly susceptible to ageing effects.

German Abstract / Deutsche Zusammenfassung

Altersbedingte Veränderungen kognitiver Leistungen sind im Bereich der exekutiven Funktionen besonders stark ausgeprägt. Zu den exekutiven Funktionen gehört unter anderem auch die Interferenzkontrolle, die die Fähigkeit irrelevante Reize zu ignorieren umfasst. Störungen der Interferenzkontrolle werden auch im Rahmen pathologischer Alterungsprozesse auffällig. Pathologisches Altern bezieht sich auf kognitive Defizite, die den Rahmen des normalen Alterns überschreiten. Dazu gehört auch die amnestische leichte kognitive Beeinträchtigung, auch amnestic Mild Cognitive Impairment (aMCI) genannt, die eine Vorstufe der Alzheimer Demenz darstellt. Veränderungen der Interferenzkontrolle spielen hier ein besonders wichtige Rolle, da Defizite in diesem Bereich u. a. Gedächtnisstörungen bei älteren Menschen mit und ohne aMCI auslösen und/oder verschlimmern können. In den letzten Jahren hat sich in vielen Studien gezeigt, dass Interferenzkontrolle keine einheitliche Funktion ist sondern vielmehr aus verschiedenen Teilfunktionen zusammengesetzt ist, die mit unterschiedlichen Aufgaben, wie z. B. der Flanker-Konflikt und der „Stimulus-Response"-Konflikt (englisch: stimulus-response conflict, SRC) Aufgabe untersucht werden können. Die einzelnen Teilfunktionen weisen darüber hinaus spezifische räumliche und zeitliche Eigenschaften der neuronalen Verarbeitung auf. In der vorliegenden Arbeit wird der Einfluss von gesunden und pathologischen Alterungsprozessen auf die einzelnen Komponenten der Interferenzkontrolle untersucht. Dazu wurden junge Erwachsene, ältere Probanden ohne kognitive Defizite und Patienten mit aMCI mit einer kombinierten Flanker-Konflikt und SRC Aufgabe untersucht. Zusätzlich wurden Untersuchungen mittels der Elektroencephalographie (EEG) sowie der funktionellen Magnetresonanztomographie (fMRT) durchgeführt. In Experiment 1 werden die Daten der fMRT-Untersuchung von 20 jungen und 19 gesunden, älteren Probanden untersucht. Die Analyse der Reaktionszeiten zeigte, dass die älteren Probanden einen größeren SRC-Effekt zeigen als junge Erwachsene. Des Weiteren ergaben sich bezüglich des Aktivierungsmusters während der Verarbeitung inkongruenter SRC-Stimuli deutliche Unterschiede zwischen den Gruppen. Ältere Probanden rekrutierten präfrontale und parietale Areale der linken Hemisphäre, während junge Probanden bei der Prozessierung der SRC-Aufgabe hauptsächlich Deaktivierungen aufwiesen. Im Gegensatz dazu löste der Flanker-Konflikt in beiden Gruppen Aktivierung im Nucelus caudatus, im okzipitalen Kortex und im Präfrontalkortex aus. Ältere Probanden aktivierten darüberhinaus parietale und präfrontale Regionen. In Experiment 2 werden die EEG-Daten von 19 jungen und 23 älteren, gesunden Probanden analysiert. Auch in dieser Untersuchung zeigte sich ein stärkerer SRC-Effekt der Reaktionszeiten bei den älteren Probanden, wobei dieser Gruppenunterschied nur in

Durchgängen mit eher langsamen Reaktionen deutlich wurde. Die Analyse der ereigniskorrelierten Potentiale P2, N2 und P3 deutet darauf hin, dass vor allem frühe Verarbeitungsstufen konfliktspezifische Gruppenunterschiede aufweisen. Die Amplitude der P2 war nur bei älteren Probanden in der inkongruenten SRC-Bedingung erhöht, während junge Teilnehmer keine Veränderung der P2 Amplitude zwischen der kongruenten und inkongruenten SRC-Bedingung zeigten. Inkongruente Flanker-Stimuli führten u. a. zu einer stärker ausgeprägten N2-Amplitude in beiden Gruppen. Dieser Unterschied war bei jungen Probanden größer als bei älteren Probanden. Weiterhin konnte eine Reduktion der P3-Amplitude durch beide Konflikttypen in beiden Gruppen festgestellt werden, wobei dieser Effekt bei älteren Probanden für beide Konflikttypen deutlich stärker ausgeprägt war. Beide Experimente deuten darauf hin, dass sich Alterungsprozesse spezifisch auf unterschiedliche Komponenten der Interferenzkontrolle auswirken. Dabei scheinen frühe Phasen der Konfliktverarbeitung ausschlaggebend für die Spezifizität der Alterungsprozesse zu sein.

Experiment 3 bezieht sich auf den Vergleich der EEG- und fMRT-Daten von jeweils 11 männlichen Probanden mit und ohne aMCI. Die Analyse der Reaktionszeiten und Fehlerraten erbrachte keine Unterschiede zwischen den jeweiligen Gruppen. Jedoch demonstrierte die Analyse der fMRT-Daten, dass die Probanden mit aMCI eine geringere Aktivierung im präfrontalen und parietalen Bereich der linken Hemisphäre in der inkongruenten SRC-Bedingung zeigten. Weiterhin konnte im Gegensatz zu den gesunden Kontrollprobanden bei der aMCI-Gruppe keine Modellierung der P2-Amplitude durch die SRC-Aufgabe festgestellt werden.

Zusammenfassend lässt sich sagen, dass die stärkere Aktivierung und Modellierung der neuronalen Korrelate, die im Rahmen gesunder Alterungsprozesse beobachtet werden konnten, eine kompensatorische Reaktion darstellen. Die Verringerung dieser Reaktion bei Patienten mit aMCI deutet darauf hin, dass pathologisches Altern mit einer „Dekompensation“ assoziiert ist. Weiterhin konnte gezeigt werden, dass die Auswirkung gesunder und pathologischer Alterungsprozesse auf Interferenzkontrolle spezifisch für die einzelnen Teilfunktionen ist. Dabei scheint die Verarbeitung der SRC-Aufgabe besonders anfällig für Alterungseffekte zu sein.

Abbreviations

µV	microvolt
ACC	anterior cingulate cortex
AD	Alzheimer's disease, Alzheimer's dementia
aMCI	amnestic mild cognitive impairment
ANOVA	analysis of variance
BA	Brodmann area
CDR	Clinical Dementia Rating
DAT	dopamine transporter
DLPFC	dorsolateral prefrontal cortex
DTI	diffusion tensor imaging
EEG	electroencephalography, electroencephalogram, Elektroencephalographie
ERP(s)	event-related potential(s)
fcsc	condition with congruent Flanker conflict and SRC information
fcsi	condition with congruent Flanker conflict and incongruent SRC information
fisc	condition with incongruent Flanker conflict and congruent SRC information
fisi	condition with incongruent Flanker conflict and SRC information
fMRI	functional Magnetic Resonance Imaging
fMRT	funktionelle Magnetresonanztomographie

GDS	Geriatric Depression Scale
HAROLD	Hemispheric Asymmetry Reduction in Older Adults
IADL	Instrumental Activities of Daily Living
IFG	inferior frontal gyrus
IOG	inferior occipital gyrus
IPL	inferior parietal lobule
NIRS	near-infrared spectroscopy
M	mean value
MFG	middle frontal gyrus
MedFG	medial frontal gyrus
MMN	mismatch negativity
MMSE	Mini Mental State Examination
MOG	middle occipital gyrus
MTL	medial temporal lobe
MWT-B	Mehrwachwahl-Wortschatz-Test B
naMCI	non-amnestic mild cognitive impairment
PASA	posterior-anterior shift in ageing
PET	positron emission tomography
PHG	parahippocampal gyrus
PIB	Pittsburgh compound B
PFC	prefrontal cortex

PostCG	postcentral gyrus
PreCG	precentral gyrus
RAVLT	Rey Auditory Verbal Learning test
RT	reaction time
RWT	Regensburger Wortflüssigkeitstest
S-S	stimulus-stimulus
S-R	stimulus-response
SEM	standard error of the mean
SFG	superior frontal gyrus
SRC	stimulus-response conflict
TAP	Testbatterie zur Aufmerksamkeitsprüfung
TMT	Trail-Making-Test
VLMT	Verbaler Lern- und Merkfähigkeitstest
WMS-R	Wechsler Memory Scale-Revised

1. General Introduction

The improvement of medical health care considerably increased life expectancy in many countries in the past years. This development has brought new challenges to our society because increased age is associated with physical and cognitive decline that can significantly reduce the quality of life of the affected individuals. Indeed, various studies illustrated that cognitive deficits – in particular executive functions such as interference control – impede activities of daily living and increase the dependency on nursing care in elderly individuals (Jefferson et al., 2006; Johnson et al., 2007). This problem is especially important when cognitive deficits exceed the normal range of ageing as found in dementia. This was shown by the World Health Report of 2003 that delineated dementia as the most important factor for disability in elderly over 60 years. Ferri and colleagues (2005) estimated that 24 million people of the world population are affected by dementia and that the number will drastically increase in the following years, reaching 81 million by 2040. Alzheimer's disease (AD) is the most common cause of dementia and thus of special importance for the demographic change of our society. Despite the dominance of memory deficits in AD, various studies found that deficits of executive functions including interference control are also evident in patients with AD and decisively contribute to problems of all-day activities (Razani et al., 2007, Marshall et al., 2011; Martyr and Clare, 2012). To ensure an early and correct diagnosis of AD it is important to understand the earliest alterations of this disease. This is why research focused on individuals with Mild Cognitive Impairment (MCI) in the past years. MCI represents a transitional state between healthy ageing and the onset of AD or other types of dementia and provides the possibility to investigate AD related alterations in the preclinical phase. Hence, it is of great importance to understand how the processing of interference control is altered with increasing age but also with the onset of pathological cognitive decline as found in MCI.

The following chapters will provide a short overview of research on healthy and pathological ageing. In this thesis healthy ageing refers to elderly with cognitive abilities that lie within the normal range of ageing, whereas pathological ageing refers to patients with MCI. Furthermore, different components as well as neural processing characteristics of interference control are introduced. At the end of chapter 1 the methodological approach and the objectives of the present thesis are discussed.

1.1. Healthy Ageing

1.1.1. Cognitive development

Ageing is accompanied by alterations of various cognitive functions. Though various studies evidence age-associated deterioration of different cognitive domains such as memory, executive functions etc., there are also functions that remain unaffected or even improve with advanced age. Park and colleagues (2002) investigated performance across different cognitive tasks in a cross-sectional study including 345 adults between 20 and 92 years. The results demonstrated that performance in tasks demanding psychomotor speed, working memory and long-term memory continuously declines from early adulthood into old age. In contrast, language abilities and word knowledge remain stable up to a high age. Other studies obtained similar results and thus corroborated the assumption that ageing particularly affects functions that can be assigned to the construct fluid intelligence while abilities reflecting crystallized intelligence are less vulnerable to ageing effects. Nevertheless, there are also studies that challenge this assumption. Schaie et al. (2004) found similar results as Park and colleagues (2002) in a cross-sectional comparison of different cognitive domains in adults ranging from 25 to 81 years. However, the analysis of longitudinal data as reported by Schaie (2005) yielded a slightly different gradient of age-related cognitive decline with later onset of cognitive deterioration and less pronounced differences of cognitive functions referring to fluid (such as processing speed, episodic memory, etc.) and crystallized intelligence (verbal abilities, word knowledge). Thus, biases related to different methodological approaches seem to influence results of cognitive ageing. Furthermore, recent studies highlighted the specificity of ageing effects on different cognitive subcomponents. These studies suggest that it is difficult to draw general conclusions about how ageing influences heterogeneous cognitive concepts such as executive functions or memory and highlight the importance of investigating how different theories of ageing apply to different cognitive operations.

There are different theoretical approaches trying to explain why certain functions decline with increasing age. Salthouse (1996b) introduced the Processing –Speed Theory that assumes that the age-associated deficits are caused by the decreased speed of various cognitive operations in elderly. Salthouse (1996b) describes two mechanisms that are responsible for the deleterious effects of slowing on different cognitive domains. The “limited time mechanism” refers to deficits that arise because the slowing of basic and/or early cognitive operations impedes the coordination of subsequent cognitive operations. Thus, complex cognitive processes that are

composed of consecutive sub-operations are particularly compromised in elderly. Furthermore, according to the "simultaneity mechanism", processing deficits can also emerge because cognitive operations in late processing stages are slowed and previously generated information is no longer accessible or already obsolete. These assumptions are based on the large body of evidence regarding decreased processing speed in elderly and the correlation of reduced processing speed with impairments of other cognitive domains (Salthouse 1991; Salthouse, 1996a; Salthouse, 1996b). Another theory focuses on the role of working memory in cognitive ageing. According to Craik and Byrd (1982) ageing is accompanied by a limitation of "processing resources" and described as "mental energy" leading to problems with self-initiated cognitive processes. Hence, tasks with high cognitive demands such as the free recall of learned information are especially affected by ageing. The term "mental energy" described by Craik and Byrd (1982) corresponds with Baddeley's concept of working memory (Baddeley, 1986). Various studies documented that working memory deteriorates with increasing age and furthermore accounts for deficits observed in tasks tapping verbal and spatial memory, speech comprehension and also reasoning and other executive functions. In contrast, Hasher and Zacks (1988) argued that the decline of inhibitory control is particularly pronounced in healthy elderly and responsible for the impairment of different cognitive domains including working memory, episodic memory, language comprehension etc. The authors argue that the capacity of the working memory is not significantly decreased in elderly. However, due to the decline of inhibition, irrelevant information can access working memory more easily and thereby limit resources for the maintenance of relevant information. Thus, the increased processing of irrelevant stimuli impedes the efficient use of relevant information for subsequent operations such as consolidation processes. The variety of theoretical approaches illustrates the complexity of age-related changes of cognition. It is unlikely that one theory covers the whole spectrum of ageing effects observed in the past years. The mechanisms proposed by different theories are probably interrelated and become more or less relevant in different contexts.

1.1.2. Neural correlates of healthy ageing

1.1.2.1. Biomarkers

Studies focusing on brain structure in the ageing brain have clearly delineated that ageing is accompanied by atrophy of different brain regions, probably due to a decrease of synapse density (Terry, 2000). The strongest structural decline can be found in prefrontal cortices whereas the parietal and the occipital cortex are only mildly affected by ageing (Resnick et al., 2003; Raz et al., 2005; Raz et al., 2004). Studies of temporal structures – in particular of the hippocampus and the parahippocampal gyrus (PHG) yield inconsistent results: some studies did not observe age-related volume decline of these anatomical structures (DeCarli et al., 1994; Sullivan et al., 1995) while other studies found reduced volumes in this brain region in healthy elderly (Golomb et al., 1993, Coffey et al., 1992; Blatter et al., 1995; Jack et al., 1992). Furthermore, existing literature suggests that age-related atrophy is more pronounced in the hippocampus than in the PHG (Raz et al., 2005). In recent years, the investigation of hippocampal subfields in the context of ageing has gained increased interest. Various studies show that particularly the subiculum and the dentate gyrus are affected by ageing (LaJoie et al., 2010; Chetelat et al., 2008). Studies investigating the correlation of structural alterations and cognitive performance in elderly yield inconsistent results. There is evidence that volume loss of the entorhinal cortex and the hippocampus is related to lower memory performance measures (Rodrigue and Raz, 2004; Rosen et al., 2003). However, correlations of other cortical areas with cognitive performance are not consistently detected.

Besides alterations of cortical tissue, ageing influences the integrity of the white matter. Pathological processes and conditions such as demyelination, microvascular disease, inflammation etc. manifest as increased signal density also called white matter hyperintensities (WMHs) in structural MRI scans (Fazekas et al., 1995; Fernando et al., 2004; Oppenheimer et al., 1995; Smith et al.,2000). The occurrence of WMH strongly correlates with increasing chronological age particularly in anterior parts of the brain and is associated with decline of executive functions, episodic memory and processing speed (Gunning-Dixon and Raz, 2000). Studies using diffusion tensor imaging (DTI) confirm the anterior-posterior gradient of white matter deterioration in healthy elderly. DTI relies on the measurement of the diffusion of water molecules. In white matter fiber tracts molecule diffusion moves along the direction of the fibers and can be quantified as fractional anisotropy.

Ageing is furthermore associated with alterations of the dopaminergic transmitter system (for review see Backman et al., 2006). The number of dopmanine D2 receptors in nigrostriatal but also in prefrontal and hippocampal areas consistently declines with increasing age. Studies that investigate dopamine receptor binding with PET or SPECT found strong correlations of D1 and D2 receptor binding with age-related alterations of psychomotor speed and executive functions but also episodic memory (Wang et al., 1998; Yang et al., 2003). Different studies demonstrated that the influence of age on performance in memory, executive, and motor tasks is minimized after controlling for dopamine receptor binding, while the correlation of D2 binding on cognitive functioning is irrespective of variations of chronological age (Volkow et al., 1998; Backman et al., 2000). These data suggest that the relationship of ageing and cognitive decline is mediated by alterations of the dopaminergic system. Furthermore, PET and SPECT studies of the dopamine transporter (DAT) - that is responsible for the dopamine reuptake in the presynaptic neuron - indicate that the DAT density strongly correlates with cognitive deficits observed in elderly participants (Yang et al., 2003; Erixon-Lindroth et al., 2005)

The Prefrontal Lobe Theory by West (1996) nicely integrates the results of behavioral and neural alterations that accompany ageing. West (1996) argued that the age-related decline of brain structure, transmitter systems etc. is particularly pronounced in the prefrontal cortex (PFC). Thus, cognitive functions that highly depend on the integrity of the PFC are especially affected with advanced age. Indeed, the ageing theories proposed by Hasher and Zacks (1988) and Craik and Byrd (1982) highlight working memory and inhibition deficits as the critical mediators of age-related cognitive decline.

1.1.2.2. Functional magnetic resonance imaging

Functional alterations in healthy elderly have received very much attention in the past years. Studies in this field detected that healthy elderly exhibit altered activation patterns when compared to young adults across many different tasks. Cabeza et al. (1997) were one of the first to show that in contrast to the predominantly left-hemispheric activation pattern in young adults, elderly exhibit bilateral activation in a verbal long-term memory task. Further evidence for the increased recruitment of bi-hemispheric neural networks in elderly was provided by studies investigating various cognitive functions including memory encoding and retrieval,

working memory, and inhibitory control (Grady et al., 2002; Reuter-Lorenz et al., 2000; Grady et al., 1998). Based on this broad body of evidence Cabeza (2002) delineated the "Hemispheric Asymmetry Reduction in Older Adults" (HAROLD) model. Moreover, Cabeza (2002) argued, that the additional recruitment serves as a compensatory mechanism to retain high performance despite the age-related decline of brain volume, transmitter systems etc. Indeed, various studies demonstrated that in particular elderly with high performance levels show increased bihemispheric recruitment, while this activation pattern is less pronounced in elderly with low performance scores (Reuter-Lorenz et al., 2000; Rosen et al., 2002; Grady et al., 2002). Nevertheless, there are also studies that revealed contrary results (Logan et al., 2002; Colcombe et al., 2003). Another age-related characteristic of neural processing was described by Davis and colleagues (2008): The hypothesis of the posterior-anterior shift in ageing (PASA) is based on findings of decreased activation of posterior brain areas such as the occipital cortex and increased recruitment of prefrontal brain regions in elderly. According to the PASA theory, the reduction of posterior activation reflects the decline of sensory processing in elderly (for a review, see Schneider and Pichora-Fuller, 2000). The increase of frontal activation is thus a necessary compensation mechanism to outweigh these deficits. In line with their theory, Davis et al. (2008) could demonstrate that the increased activation of the PFC in elderly correlates with performance scores in a memory retrieval task and furthermore correlates with age-related activation decrease in occipital regions. The dedifferentiation theory proposed by Baltes and Lindenberger (1997) provides an explanation for the increased demand of compensatory neural mechanism in elderly. The theory assumes that the functional specificity of different cognitive mechanisms diminishes with increasing age. Correspondingly, the correlation of performance scores representing different cognitive domains increases in late adulthood indicating that different cognitive functions increasingly rely on common cognitive mechanisms and also on common neural substrates (Mitrushina and Satz, 1991; Baltes and Lindenberger, 1999). Additionally, Park and colleagues (2004) found that in a face processing task elderly adults exhibited increased activation of areas that are not specifically associated with face processing (such as the PHG). This "diffuse" activation pattern in elderly was also demonstrated in other tasks (Goh et al., 2010; Grady et al., 1994).

1.1.2.3. Event-related potentials

Ageing is associated with various alterations of event-related potentials (ERPs). Very early ERPs such as the N1 and the P1 reflect early sensory processing and are modulated by stimulus characteristics such as stimulus color, brightness, loudness etc. Different studies revealed that ageing is accompanied by an increase of P1 and N1 amplitude (for a review, see Kok and Zeef, 1991). Moreover, the modulation of both components in response to alterations of stimulus features seems to be more pronounced in healthy elderly (Kramer et al., 1996). Studies of the mismatch negativity (MMN) additionally reveal ageing effects on early processing stages. The MMN is usually triggered by auditory and visual oddball tasks and appears between 100 – 200 ms after stimulus onset. This temporal phase is associated with pre-attentative processes that are activated by the mismatch of the incoming sensory signal and the signal expectations formed by the participant due to the regularities of the previous stimuli. A variety of studies demonstrated that the MMN is reduced in elderly when compared to young controls (Woods, 1992; Czigler et al., 1992; Pekkonen et al., 1993). The influence of ageing on later ERPs such as the N2 and the P3 is heterogeneous because there are different subtypes of both components that reflect different cognitive processes.

The N2 component is characterized by a negative peak occurring about 250-300 ms after stimulus onset and can be subdivided to different subcomponents (for review, see Folstein and Van Petten, 2008). The amplitude of the anterior N2 component is increased in response to novel stimuli, e. g. stimuli that deviate from a standard stimulus set, possibly indicating cognitive mechanisms associated with mismatch detection and orienting. This novelty response was found to be decreased in healthy elderly reflect by a decreased N2 amplitude modulation (Czigler and Balasz, 2005; Riis et al., 2009). In contrast to the anterior N2, the posterior N2 is sensitive to the predictive information of a stimulus as found in valid vs. invalid cues (Suwazono et al., 2000). Furthermore, the N2pc (posterior-contralateral) represents a negativation that appears contralateral to presentation side of a stimulus in visual search tasks. The N2pc indexes visuospatial shifting of attention and is attenuated and delayed in elderly participants (Hopf et al., 2004; Lorenzo-López et al., 2011).

The novelty P3 or P3a that is induced by task-irrelevant, new stimuli is located over frontal electrodes and shows a maximum peak between 300-600 ms after stimulus onset over frontal electrodes (Fabiani and Friedman, 1995). The novelty P3 reflects cognitive processes associated with orienting and is modulated by the presentation of repeated or novel stimuli

(Friedman et al., 1998). This amplitude effect is however not evident in elderly participants (Friedman and Simpson, 1994; Friedman et al., 1998). In contrast the P3b component is associated with the allocation of attentional resources and context updating (Donchin, 1981; Fabian et al., 1986) and has a more posterior orientation than the novelty P3. Several studies found that both components rely on distinct neural networks (Baudena et a., 1995; Bledowski et al., 2004; Polich, 2003). Various studies found that the P3b amplitude is decreased in healthy elderly across different task designs. The P3b latency is increased in elderly, however, age-related differences are modified by different factors, such as the sensory modality, intensity, and complexity of the stimulus material employed in the respective studies (for review, see Polich, 1996). Furthermore, the P3b topography differs between young and elderly participants indicating age-related modifications of the underlying neural generators (Friedman et al., 1997).

1.2. Pathological Ageing

1.2.1 Classification and diagnosis criteria

The term MCI describes cognitive deficits that exceed the normal range of ageing. It thus includes individuals whose cognitive performance lies below age and education adjusted mean values. MCI is considered to represent the transitional stage between normal ageing and the onset of dementia and thus offers the possibility to investigate very early pathological alterations associated with different neurodegenerative conditions such as the AD.

The term MCI was introduced by Reisberg et al. in 1988 and referred to stage 3 of the Global Deterioration Scale, a rating scale that subdivides the process from normal cognitive ageing with no cognitive deficits to severe dementia into seven stages (Reisberg et al. 2007). The stage 3 of the GDS was formerly termed “mild cognitive decline” and included individuals with memory deficits that can only be diagnosed by “thorough examination“ (GDS, Reisberg et al., 1988). A few years earlier the Clinical Dementia Rating (CDR) was published and offered another means to evaluate the cognitive status of healthy and impaired elderly. A CDR score of 0.5 corresponds with stage 3 of the GDS and is characterized by a “mild consistent forgetfulness” with mild or doubtful impairment of daily functioning. Both scales are widespread tools in clinical and experimental settings to rate the severity of cognitive decline, however, Petersen emphasized that these rating scores do not fully accord with the current

concept of MCI, because patients with early AD might also fall into this category. Moreover, in the past years scientists also introduced other terms and concepts than MCI when investigating the prodromal stages of dementia. Kral (1962) for example described the "benign senescent forgetfulness" as a deficit to recall remote information. Further concepts were introduced by Crook and colleagues (1986; "age-associated memory impairment"), by Graham et al. (1997; "cognitive impairment no dementia"), and by different institutions such as the International Psychogeriatric Association and World health Organization (Levy, 1994; "ageing-associated cognitive decline") These concepts are based on different diagnostic criteria and included cognitive alterations that lay within and beyond the normal range of ageing.

The diagnostic entity MCI was continuously adapted and the diagnostic criteria were revised in recent years. Different subtypes of MCI with distinctive profiles of cognitive impairment have also been identified (Petersen, 2004; Winblad et al., 2004; see *Figure 1*): 1) single-domain aMCI (sdaMCI), 2) multiple-domain aMCI (mdaMCI), 3) single-domain naMCI, and 4) multiple-domain naMCI. Diagnostic criteria for aMCI were defined by Petersen et al., (1995) and modified in the following years (Petersen et al., 1999; Petersen et al., 2001). They include: 1) memory complaint, preferably corroborated by an informant; 2) objective memory impairment; 3) normal general cognitive function; 4) intact activities of daily living; and 5) not demented.

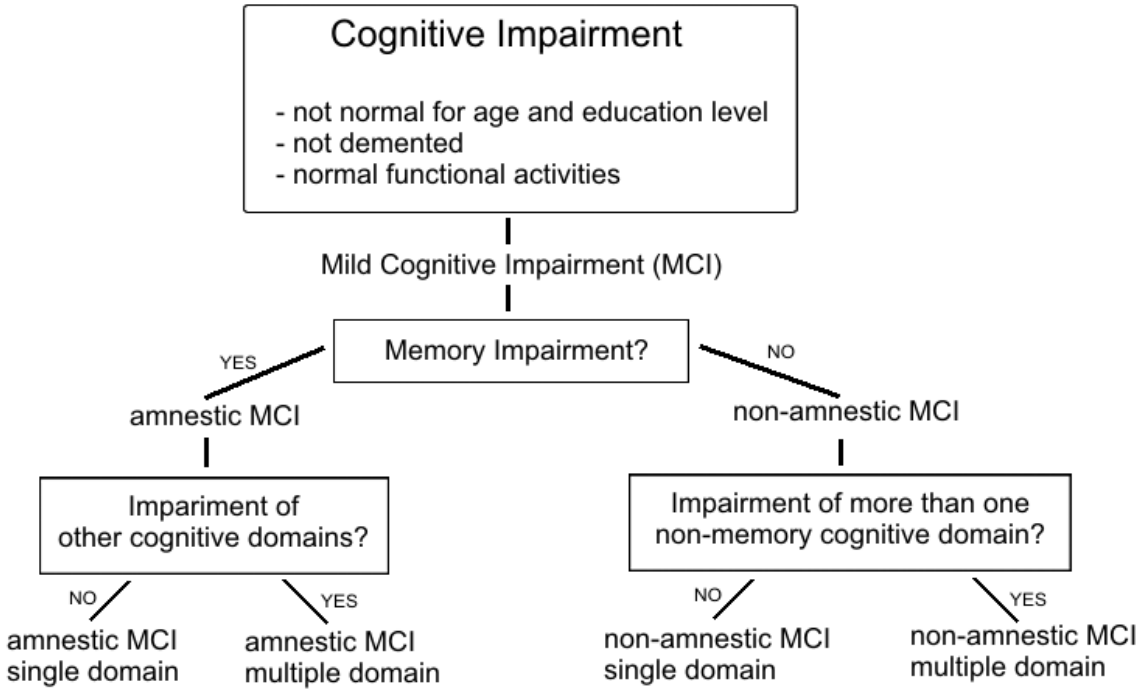

Figure 1 Schematic depiction of the different subtypes of Mild Cognitive Impairment according to Petersen (2004)

MCI was included in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM 5). The DSM 5 differentiates between the severity (*major neurocognitive disorders* and *minor neurocognitive disorders)* and the etiology of cognitive deficits (AD, frontotemporal lobar degeneration, Levy body disease, vascular disease, etc.). The diagnostic criteria for *minor neurocognitive disorders* are met when modest performance decline in one or more cognitive domain is reported by the patient (or friend/family member) and confirmed by standardized neuropsychological testing. Furthermore, activities of daily living are not impaired and cognitive deficits cannot be explained by delirium or other mental disorders.

Scientific attention particularly focuses on aMCI because it is considered to represent the preclinical stage of AD, the most common cause of dementia (Fratiglioni et al., 2000). Indeed, annual rates of cognitive decline to AD range from 7-8 % to 41 % in individuals with aMCI (Geslani et al., 2005; Mitchell and Shiri-Feshki, 2009; Larrieu et al., 2002); whereas only 1-2 % of the general population develop AD in the same period. In contrast to aMCI, naMCI is assumed to precede other types of dementia such as the frontotemporal dementia. Though the conversion to AD is not strictly confined to a certain MCI subtype, results indicate that aMCI is associated with a higher risk of AD than naMCI (Busse et al., 2006).

Despite the efforts to define specific diagnostic criteria, aMCI remains a heterogeneous entity. Importantly, not every person with aMCI declines to AD. Around 50% of individuals meeting the criteria for aMCI exhibit stable performance levels over 2-3 years or even revert to a normal cognitive status (Larrieu et al., 2002). Thus, not only neurodegenerative processes seem to contribute to the impairments detected in individuals with aMCI, but also other factors such as psychiatric conditions, changes of hormonal balance, vascular diseases, etc. that do not elicit progressive cognitive decline. Furthermore, there are no strict recommendations regarding the neuropsychological evaluation of cognitive deficits, thus, the classification of MCI possibly differs between different clinical and experimental settings due to the number and selection of standardized neuropsychological tests.

1.2.2 Neural correlates of aMCI

1.2.2.1 Biomarkers

Various studies document that neuropathological alterations that are typical of AD can already be detected in aMCI. They thus corroborate the assumption that aMCI represents the prodromal phase of AD.

One major finding in patients with AD is the marked neural loss in the medial temporal lobe (MTL) including the hippocampus, the entorhinal, and the perirhinal cortex. Slight atrophy in these regions can already be detected in individuals with aMCI (Convit et al., 1997) and furthermore predicts the conversion to AD (Jack et al., 1999; Korf et al., 2004; Tapiola et al., 2008). Recent studies concentrated on the role of single subfields of the hippocampus in the differentiation of healthy ageing, aMCI, and AD. Available studies (Yassa et al., 2010; La Joie et al., 2013; Yushkevich et al., 2015) showed that volume differences between elderly with and without aMCI are particularly pronounced in the CA1 region, while other parts of the MTL do not consistently differ between both groups. Apostolova et al. (2006) additionally confirmed that particularly neural loss in the CA1 region but also in the subiculum is critical for the conversion from aMCI to AD.

Furthermore, amyloid deposits are another important biomarker of AD and also occur in individuals with aMCI. The development of different PET (positron emission tomography) ligands such as the Pittsburgh compound B (PIB) (Klunk et al., 2004) has enabled the investigation of amyloid depositions in vivo. Studies in this field observed, that aMCI is associated with PIB retention that lies between AD and healthy ageing (for review see Rabinovici and Jagust, 2009). However, individual investigation of patients with aMCI revealed that the uptake of PIB is bimodal, that means that most aMCI patients either exhibit levels of PIB binding that resemble AD or healthy ageing while only few aMCI patients show intermediate PIB uptake (Kemppainen et al., 2007). Importantly, elevated PIB uptake is more common in aMCI (52% - 87%) than normal PIB binding (Rabinovici and Jagust, 2009). Amyloid imaging is furthermore used to predict the progression of aMCI to AD. Several studies revealed that individuals with increased PIB uptake have a higher risk to develop AD in the following months and years (Forsberg et al., 2007; Okello et al., 2009).

Besides amyloid plaques, neurofibrillary tangles (NFT) are another diagnostic marker of AD. Braak and Braak (1991) identified six stages of NFT distribution in the evolution of AD,

whereas individuals with aMCI usually correspond to the Braak stages II and III (Petersen et al., 2006) that are mainly characterized by NFTs in the MTL. Correspondingly, Markesbery et al. (2006) detected that the number of NFTs is increased in patients with aMCI in the entorhinal cortex, the CA1 region of the hippocampus, the subiculum, and the amygdala but also in the IPL compared to elderly with no cognitive deficit. According to Braak and Braak (1991) the expansion of NFTs to neocortical structures indicates the onset of full AD symptomatology. Thus, the study by Markesbery (2006) possibly included subjects with progressed aMCI or very early AD. The amount of NFTs in the MTL region furthermore correlates with memory scores and thus probably contributes to memory deficits in individuals with aMCI (Guillozet et al., 2003).

AD is additionally associated with decreased glucose metabolism particularly in the MTL region but also in other cortical areas including the prefrontal, parietal and cingulate cortex (Mosconi et al., 2005). In individuals with aMCI reduced glucose metabolism is particularly pronounced in the hippocampus and adjacent regions, while alterations in other cortices seem to be related to AD (Drzezga et al., 2003). The pattern of metabolic reduction differs between aMCI patients who develop AD in the following months. These patients exhibit reduced glucose metabolism in temporo-parietal regions and the posterior cingulate cortex in comparison to patients with stable clinical symptoms (Drzezga et al., 2003; Chetelat et al., 2003; Anchisi et al., 2005).

1.2.2.2. Functional magnetic resonance imaging

Research on functional differences between elderly with and without aMCI mainly focuses on memory functions investigated with verbal and non-verbal encoding and recognition tasks. A considerable part of these studies revealed that patients with aMCI exhibit enhanced activation of the MTL region (Hämäläinen et al., 2007; Dickerson et al., 2005; Miller et al., 2008) while other studies detected decreased activity in aMCI patients in these areas (Machulda et al., 2003; Small et al., 1999). These inconsistencies are possibly based on different clinical features of the patients investigated in the respective studies. Dickerson et al. (2005) hypothesized that increased recruitment of neural resource can be evidenced in aMCI patients with rather mild deficits, while individuals with aMCI that already exhibit progressed cognitive decline show decreased activation when compared to healthy controls. The accumulation of pathological

alterations such as neural degeneration possibly causes the turning point of additional recruitment in the hippocampal region in aMCI. In line with this hypothesis, Celone et al. (2006) confirmed that the increased/decrease of hippocampal activation is specific for different stages of cognitive decline in patients with aMCI.

The relation of hippocampal activity and memory dysfunction in aMCI is not fully understood. it is highly debated whether hyperactivation of the hippocampus has a beneficial effect on memory performance or whether it interferes with successful memory encoding and retrieval. Gron and colleagues (2006) found that the acetylcholinesterase inhibitor galantamin elicited increased activation of occipitotemporal areas including the hippocampus, the PHG, and the FFG. aMCI patients additionally exhibited better performance rates in a word learning task under the treatment. The authors argued that the increased hippocampal activation might be associated with memory improvement. However, there is also evidence challenging the view that increased activation of the hippocampus has a beneficial effect on memory performance in aMCI. Following studies that modulated hippocampal activity and memory performance in rodents (Koh et al., 2010), Bakker and colleagues (2012) administered an anti epileptic drug (levetiracetam) to patients with aMCI in order to reduce hyperactivation of the hippocampus. Indeed, they found that levetiracetam attenuates hippocampal activity to a normal level and moreover improves performance in a three choice memory task in subjects with aMCI. The authors argued that the increased activation of the hippocampus does not represent compensatory mechanisms but rather reflects the progression of cognitive decline in aMCI. Moreover, different studies found, that increased activation of the MTL region is associated with cognitive decline in the following years. The inconsistent findings of hippocampal activation modulation possibly go back to different baseline activation levels in the investigated samples.

Studies that focus on other cognitive functions than memory additionally find increased recruitment of different neural networks (Kaufmann et al., 2008; Li et al., 2009). However, in contrast to healthy ageing additional activation seems to become less efficient in elderly with aMCI. Additional recruitment in healthy elderly is frequently detected in areas that are closely related to the investigated function, e. g. when young adults elicit activation of the left PFC, healthy elderly additionally recruit homologue regions of the other hemisphere (Cabeza et al., 1997). In contrast, available studies suggest, that the additional recruitment of neural resources is less specific in subjects with aMCI: a study comparing the activation pattern during a location and a face matching task in elderly with and without aMCI found that healthy elderly

specifically activated areas along the dorsal vs. the ventral pathway in the respective tasks while elderly with aMCI showed mixed activation patterns in both conditions (Bokde et al., 2008). In addition, Kaufmann and colleagues (2008) observed that patients with aMCI elicited increased activation of the occipital cortex and the MTL region in response to the Stroop conflict, a task that is usually associated with prefrontal and parietal activation.

Taken together, hyperactivation of the hippocampus but also of other brain areas seem to be a typical finding in aMCI. However, the role of this activity increase is controversial. The relation of hippocampal activity is closely related to the memory impairments of aMCI, nevertheless, it is unclear whether the overrecruitment represents beneficial or detrimental effects on mnemonic functions. In general, additional neural recruitment seems to become less specific.

1.2.2.3. Event-related potentials

Electrophysiological studies additionally detected sensitive indicators of altered cognitive processes in aMCI and early AD. Existing research focused on different ERPs and revealed that already early processing stages, e. g. reflected by MMN are altered in individuals with aMCI: Several studies found that the MMN amplitude is decreased in individuals with aMCI when compared to healthy controls (Golob et al., 2002; Mowszowski et al., 2012; Lindin et al., 2013). This decrease possibly reflects deficits of the automatic comparison of deviant stimuli to the concept of the standard stimulus, possibly because the memory trace of the standard stimulus set is inaccurate or incomplete in aMCI. Furthermore, MMN amplitude shows a stronger decline in elderly with aMCI than in healthy controls (Lindin et al., 2013). In contrast, an increase of the MMN in individuals with aMCI and AD relative to healthy controls was observed by Tales and colleagues (2008). Despite these inconsistent findings, these studies clearly indicate the important role of early, automatic processes in the differentiation of healthy ageing and the onset of aMCI.

Further ERP studies focused mainly on the N2 and the P3 component. Both components are characterized by an amplitude reduction and a latency delay in patients with early AD (Frodl et al., 2002). However, studies including individuals with aMCI yield inconsistent results. Lai and colleagues (2009) found that P3 latency is delayed in AD and MCI patients (inclusion criteria for MCI also encompassed non-amnestic deficits), in contrast, the N2 component did not differ

significantly between the groups. P3 prolongation was even more pronounced in a follow-up examination after one year, while clinical performance scores remained stable. These results indicate that the P3 reflects disease progression more sensitively than standardized clinical tests. However, other studies emphasize the role of the N2 component for the correct discrimination of elderly with and without aMCI. Cid-Fernandez et al. (2014) detected reduced N2 amplitudes in aMCI subjects in response to a Go/NoGo task, while there were no group differences of the P3 component. In addition, according to Papaliagkas et al (2011) the N2 component reflects general cognitive performance in early stages of aMCI more precisely than the P3 component. Findings of delayed N2 latencies in aMCI patients who develop AD in the following year compared to patients with stable symptomatology additionally indicate the importance of the N2 component prediction of disease progression (Bennys et al., 2011).

Electrophysiological correlates of word and memory processing such as the N400 and P600 seem to be altered in individuals with aMCI as well. The N400 is a sensitive marker of semantic violations while the P600 is associated with information encoding and retrieval. The modulation of the P600 and the N400 induced by repetition of the experimental stimuli is markedly altered in elderly with aMCI compared to healthy controls (Olichney et al., 2002). This repetition effect additionally was able to discriminate aMCI patients that convert to AD and patients that do not show progressive memory decline.

1.3. Interference control

The term interference control refers to the ability to attend relevant stimuli and to ignore irrelevant information. To investigate mechanisms of cognitive control different conflict tasks like the Flanker or Simon paradigm are frequently employed. The Flanker task usually consists of a target stimulus (“F” or “G”) that requires a certain response (“F” for left key press, “G” for right key press). The target stimuli are surrounded by two or more distractors that can be congruent or incongruent to the central target. In congruent trials flanker stimuli are the same as the target stimuli (“FFF”). Incongruent trials contain distracting stimuli which are associated with a different response (“GFG”). In incongruent trials subjects typically show increased response costs indicated by higher reaction times (RT) and error rates in comparison to congruent trials. Another paradigm triggering conflict situations is the Simon task. In this task subjects have to respond to a stimulus with either a right or left key press (“F” for left key

press, “G” for right key press). These stimuli usually contain spatial information, for example through lateralized presentation. Though spatial information is irrelevant for task performance, it interferes with response selection. RTs are faster and error rates are lower on compatible trials, namely when target associated response side and spatial information match (“F” presented on the left side). Incompatibility is characterized by mismatch of appropriate response side and spatial attributes associated with the target stimuli (“F” presented on right side). According to the dimensional overlap model by Kornblum and colleagues (1990) the Flanker and Simon conflict represent different types of conflicts namely, stimulus-stimulus (S-S) and stimulus-response (S-R) conflicts. The Flanker or S-S conflict arises due to an overlap of the relevant and the irrelevant stimulus dimension. Because of this overlap, stimulus presentation triggers two competing stimulus-identification processes of which only one can be chosen for further response activation. In contrast, S-R conflicts such as the Simon conflict are based on an overlap of the irrelevant stimulus dimension (e. g. presentation side) and the response set (reaction side). In this case, the presentation of the (irrelevant) stimulus automatically triggers activation of the associated response (stimulus presented on the left side leads to activation of reaction the left side). In contrast, the relevant dimension (e.g. Letter category) does not overlap with the response set and thus response activation is guided by “response identification” processes which are more time-consuming than automatic activation. There is in ongoing debate about whether S-S- and S-R conflicts represent independent conflict types that are processed in different stages. Simon and Berbaum (1990) found that the Simon and Stroop conflict do not interact with respect to behavioural measures (reaction time) when both conflicts occur at the same time. That means that the increase of reaction time in response to double conflict trials equals the addition of the respective single conflict effects. Referring to the additive-factor method by Sternberg (1969), the authors argued that the lack of an interaction signifies that both conflicts are processed in different stages. Similar results were obtained by Frühholz et al. (2011) who also found no interaction of behavioural S-S and S-R conflicts in a combined Flanker and Simon task.

Besides behavioural measures other methodological approaches such as EEG and functional magnetic resonance imaging (fMRI) are employed to investigate the neural mechanisms underlying both conflict types in order to find potential spatial and temporal dissociations in the processing of the s-s and s-r conflict.

1.3.1. Functional magnetic resonance imaging

There is a huge body of evidence that different conflict tasks frequently elicit activation of the dorsolateral PFC (DLPFC), the anterior cingulate and also of parietal regions such as the precuneus and inferior parietal lobule (IPL) (Nee et al, 2007). A meta-analysis showed that the Flanker conflict is mainly associated with activity in the DLPFC and the insula of the right hemisphere while the SRC induce increased activation of the precuneus, anterior cingulate and the premotor cortex (Nee et al, 2007). Studies that investigate different conflict types in the same experimental setting also find that distinct neural networks underlie S-S and S-R conflict processing. The investigation of a combined Flanker and Simon task with fMRI revealed that although both conflicts elicit activation in areas that are commonly associated with conflict processing such as the cingulate gyrus and the dorsolateral PFC, that activation patterns triggered by S-S and S-R conflicts do not overlap (Frühholz et al., 2011). Accordingly, Egner and colleagues (2007) found distinct activation clusters in response to the Simon and the Stroop conflict. The authors argued that the resolution of both conflict types relies on different cognitive mechanisms. The signal increase in the superior parietal cortex in incongruent Stroop trials reflects mechanisms associated with stimulus-biasing in favour of relevant stimulus information. In contrast, the activation of the premotor cortex in the incongruent Simon condition indicates a response-biasing strategy, that means, the inhibition of response activation related to the irrelevant information. In contrast, a study by Fan and colleagues (2003) revealed that besides conflict-specific activation patterns, the Flanker, the Stroop and the Simon conflict also elicit overlapping activation in the anterior cingulate cortex (ACC and the DLPFC). However, the analysis of the behavioural data yielded no significant correlation between the respective conflict effects. The authors thus argued that particularly the ACC possibly plays a passive role in conflict processing (e. g. conflict detection) and that the cognitive mechanisms critical for conflict resolution are processed in the areas specifically activated by the respective conflicts.

1.3.2. Event-related potentials

ERP studies provide information about the temporal characteristics of interference control. In accordance with fMRI studies, ERP research corroborates the assumption that both conflicts elicit differentials effects on different temporal processing stages. Frühholz et al. (2011)

demonstrated that an early N2-earlyP3 complex is modulated only by the Flanker conflict, while the Simon task enhances the amplitude of the later P3b component. Double conflict trials were associated with amplitude effects in both time frames. These data suggest that different cognitive mechanisms contribute to the processing of S-S and S-R conflicts. The elevated P3b amplitude in response to incongruent S-R conflict trials is thus possibly associated with an increased demand to continuously update information about stimulus-response mapping. In contrast, more pronounced N2-earlyP3 amplitudes in the incongruent Flanker condition possibly reflect a stronger implementation of inhibition regarding the representation of the irrelevant Flanker stimuli. Further evidence for the differential effects of S-S and S-R conflict on different processing stages is provided by Li et al. (2014) and Wang et al. (2014). Li et al (2014) report that in a Simon-spatial-Stroop task the N2 amplitude is increased in response to both conflict types. In double conflict trials the N2 amplitude modulation shows no interaction of the single conflict effects, that means the S-S and the S-R conflict showed an additive effect on the N2 amplitude. Wang et al. (2014) employed a similar Simon-spatial-Stroop task and additionally a Simon-color-Stroop task in their study, however, different conflict types were investigated "separately" without a double conflict condition. They found that in both tasks that S-S conflict-induced N2 amplitude effects occur earlier than the S-R related modulation. However, temporal processing characteristics are similar for both conflict types in later processing stages indexed by the P3. Furthermore, the study demonstrated that the S-R conflict has a stronger effect on the P3 amplitude than the S-S conflict. These studies accord with the assumption of independent S-S and S-R related cognitive mechanisms. Though, distinctive ERP effects are not necessarily linked to independent cognitive mechanisms, it can be assumed that common resources would result in stronger interaction effects across different studies. These studies additionally show that the effects of different conflict types on different processing stages also depends on task design and stimulus material, since single conflict effects were study specific. Nevertheless, in line with Kornblum and colleagues (1990) these studies suggest that (sub-operations of) S-S conflicts seem to be processed earlier than S-R conflicts.

1.4. Methods

1.4.1. Study design

Every participant first underwent neuropsychological testing and then took part in the electroencephalogram (EEG) and fMRI study. The succession of the EEG and fMRI session was counterbalanced. The study design was equivalent for both experimental sessions and is described in the following sections. Specific modifications due to different methodological approaches are described in the method section of each experiment.

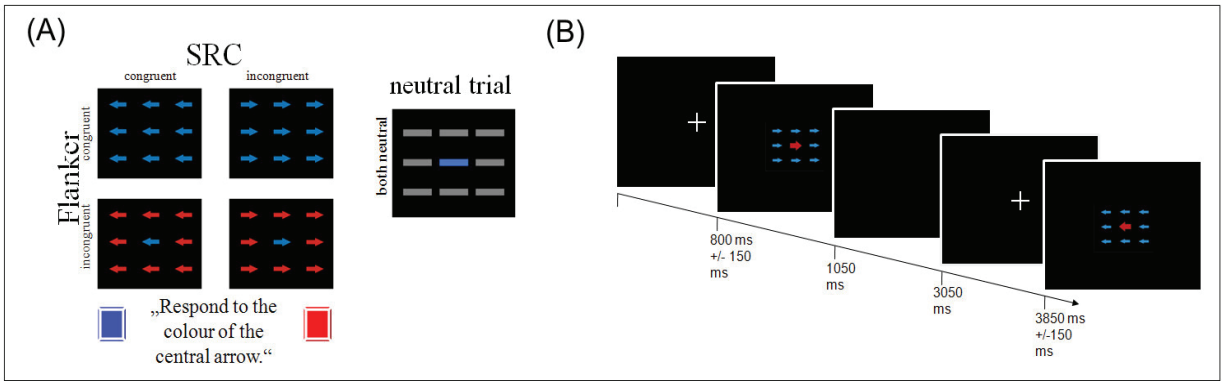

Figure 2 Schematic depiction of A) the stimulus material for the different experimental conditons and B) the trial sequence.

The stimulus material consisted of nine arrows arranged in three rows (see *Figure 2*). The participants were instructed to attend to the color of the central arrow (blue or red) and to react as fast as possible via right or left button press with their index finger. The arrows surrounding the central target could either have the same color as the target (congruent Flanker condition) or the color allocated to the opposite response side (incongruent Flanker condition). Furthermore, all arrows were either oriented to the correct response side as indicated by the color of the central arrow (congruent SRC condition) or pointed to the opposite direction (incongruent SRC condition). Thus, there were four experimental conditions: 1) congruent Flanker and SRC condition (FcSc); 2) incongruent Flanker and congruent SRC condition (FiSc); 3) congruent Flanker and incongruent SRC condition (FcSi), and 4) incongruent Flanker and SRC condition (FiSi). Stimuli were presented in six blocks of 60 trials separated by short breaks of 10 seconds. There were 72 trials of each condition. Trial sequence was pseudo-randomized to avoid effects of trial succession. Each trial started with a white fixation cross on black background in the center of the screen (800 ± 150 ms). Thereafter, the set of arrows appeared for 250 ms followed by a blank screen for 2000 ms.

1.4.2. Neuropsychological testing

Neuropsychological assessment included the tests listed in *Table 1*. The assessment lasted about 90 minutes and covered memory, executive, attentional and visuo-constructive functions. The diagnosis of memory deficits and thus the classification of aMCI was based on the performance in the "Verbaler Lern- und Merkfähigkeitstest" (VLMT; Helmstaedter et al., 2001), a german version of the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964).

Table 1 Overview of the tests employed in the neuropsychological evaluation.

Cognitive Domain	Test	Source
Level of general cognitive functioning	Mini-Mental-State Examination	Folstein, 1975
Verbal Intelligence/ pre-morbid intelligence level	Mehrfachwahl-Wortschatztest B (multiple choice vocabulary Test)	Lehrl, 1995
Verbal memory	Verbaler Lern und Merkfähigkeitstest (VLMT) (german version of the RAVLT)	Helmstaedter et al., 2001
Non-verbal memory and visuospatial abilities	Rey Complex Figure Test	Rey, 1941
Attention and executive functions	Alertness; Divided Attention (from „Testbatterie zur Aufmerksamkeits-Prüfung; computer based test battery for attention)	Fimm and Zimmermann, 2001
	Trail-Making-Test	Reitan, 1992
	Digit Span; Block Span (from Wechsler Memory Scale Revised)	Härting et al., 2000
	Regensburger Wortflüssigkeitstest (word fluncy test; semantic category: "animals", phonological category: words beginning with "S")	Aschenbrenner et al., 2001
Mood	Geriatric Depression Scale (GDS)	Yesavage et al., 1982
Activities of Daily Living	Alters-Alltagsaktivitäten-Skala (from Nürnberger Alters-Inventar, NAI; Scale of daily activities for elderly)	Oswald and Fleischmann, 1995
	Instrumental Acitivities of Daily Living	Lawton and Brody, 1969

The VLMT is a word list learning test including two lists with 15 items respectively. In the trials 1-5 the first word list is read to the participant, who is instructed to memorize the words and recall them in no special order. Afterwards in the interference trial, the second list is presented with the same instructions. Immediately after the interference trial, the participant is asked to recall the first word list without another presentation (6th trial). This recall trial is repeated after 30 minutes (7th trial). Finally, in the recognition trial the participant has to identify the words of the first list out of 60 verbally presented items. These 60 items also include words of the interference list and distractor words that are semantically or phonologically related to the words of both wordlists.

1.4.3. Electroencephalogramm and event-related potentials

The EEG is based on voltage differences measured with electrodes on the scalp over time. These voltage differences result from synaptical activity of pyramid cells that are arranged perpendicularly in the cortex. When the apical dendrites of the pyramid cells receive an excitatory impulse, a relative negativity evolves in the extracellular space of the apical dendrites also called excitatory postsynaptic potential. In contrast, inhibitory postsynaptic potentials are characterized by a positivity in the area of the apical dendrites. When many postsynaptic potentials summate, signal power increases and the voltage deviation can be detected at the scalp. ERPs are generated by averaging EEG signal intervals matched to the onset of a stimulus or a response. Signal averaging reduces signal noise and discloses voltage differences that result from brain activation associated with the presented stimulus or the executed response.

1.4.4. Functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging provides the possibility to indirectly measure neural activity. Participants are positioned in a strong magnetic field that aligns the hydrogen nuclei in the direction of the magnetic field. The nuclei can absorb energy applied by radio frequency (RF) impulses and also release energy that can be detected by RF coils in the MRI scanner. fMRI relies on the BOLD effect (“Blood-oxygenation level dependent”-effect), the modification of the MR signal due to different levels of blood oxygen (Frahm et al., 1992;

Kwong et al., 1992; Ogawa et al., 1992): Neuronal activity is associated with an increased consumption of glucose and oxygen which leads to an increase of regional blood flow to ensure adequate supply of the brain tissue. The increase of regional cerebral blood flow is associated with the enrichment of oxygenated hemoglobin, which has different magnetic properties than deoxygenated hemoglobin. The BOLD signal follows a certain principle that is described by the hemodynamic response function (HRF). The HRF starts with the "initial dip" that represents the initial decrease of oxygenated hemoglobin. With a lag of a few seconds the BOLD signal increases due to overcompensatory supply of oxygenated hemoglobin and peaks after about 6-8 seconds after the onset of neural activity. Afterwards the signal reverts to the baseline level (Heeger and Ress, 2002). The HRF is used to calculate models that estimate the signal time course according to the onset of the experimental stimuli/manipulation for every investigated voxel.

1.4.5. Legal frame work and study preparation

The experimental design and procedure of the studies reported in the following sections corresponds with the guidelines of the declaration of Helsinki and was furthermore approved by the local ethics committee of the University of Bremen. Every participant was informed about the general study procedure and the potential risks of fMRI and EEG recording, instructed about their right to terminate study participation at any time point, and gave written consent to take part in the study (see Appendix).

1.5. Objectives of the present thesis

The age-associated decline of executive functions such as interference control was described by Hasher and Zacks (1988). Various studies suggest that interference control does not reflect a unitary function but is rather composed of different subcomponents represented by different conflict tasks. These components rely on different networks located in prefrontal and parietal areas and furthermore exhibit distinctive temporal characteristics of neural processing. The specificity of neural correlates associated with different conflict types raises the question whether ageing equally or differentially affects these distinct components. In Experiment 1 and 2 the combined SRC and Flanker conflict task is conducted by healthy elderly and young

controls during fMRI end EEG recording to investigate whether ageing has specific effects on the spatial and temporal correlates of neural processing associated with the respective conflicts.

Hasher and Zacks (1998) furthermore delineated that deficiencies of interference control can impede other cognitive domains such as memory functions. This is particularly relevant for elderly with aMCI because impaired control mechanisms possibly aggravate their memory dysfunctions. Thus, Experiment 3 investigates the processing of the SRC and the Flanker conflict in elderly with aMCI in comparison to healthy controls. In addition, the acquisition of EEG and fMRI data (in separate sessions) enables to investigate whether activation patterns and different processing stages of interference control are changed in aMCI:

2. Experiment 1

The data of the present study were published in an original research article:

Korsch, M., Frühholz, S., Herrmann, M. (2014). Ageing differentially affect neural processing of different conflict types. *Front Aging Neurosci*, 6:57. (doi: 10.3389/fnagi.2014.00057).

This chapter is an excerpt of this publication. Due to overlapping content with previous chapters of this thesis, some sections of the published article were omitted.

2.1. Introduction

Various neuroimaging studies have proved that elderly participants show increased activation in frontal and parietal areas when faced with incongruent information in conflict tasks (Langenecker et al., 2004; Zysset et al., 2007; Milham, 2002; Lee et al., 2006). These findings are in line with cognitive ageing theories stating that elderly employ compensatory neural mechanisms to compensate for an age-related cognitive decline. However, data from several studies challenge the frontal lobe hypothesis and the compensatory hyperactivation hypothesis, and cast doubt on the idea that this theory equally applies for all cognitive functions associated with the PFC. West and Alain (2000) used a Stroop task and demonstrated that the processing of distractors was impaired in elderly, while the processing of the target stimulus remained intact. Importantly, both conflict resolution processes were associated with an EEG signal source in the PFC. Furthermore, a recent meta-analysis (Turner and Spreng, 2012) on inhibition and working memory revealed that age-related differences of neural processing differ depending on the respective cognitive domain. While working memory was characterized by increased activation of DLPFC, supplementary motor area (SMA) and IPL in elderly, age-related differences in inhibition processing became evident in the inferior frontal gyrus (IFG) and the pre-SMA. These findings indicate that cognitive ageing is not associated with a general mechanism leading to a compensatory increase in PFC activity but rather by a specific modification of the neural networks involved in the processing of a certain task or task component. As this meta-analysis summarizes studies that used different types of conflict tasks (e. g. Flanker task and Simon task) no information is provided about conflict specific ageing effects.

With respect to conflict resolution in elderly subjects, there is further evidence for a dissociation of ageing effects on interference control. With regard to behavioural performance, it has been shown that elderly participants show higher congruency effects compared to young participants during the Simon task (Kubo-Kawai and Kawai, 2010; van der Lubbe and Verleger, 2002), while Flanker effects do not differ between young and old participants (Nieuwenhuis et al., 2002; Falkenstein et al., 2001). These data indicate that conflicts in the response selection stage are particularly vulnerable to age-associated changes in inhibition control. Furthermore, Sebastian and colleagues (2013) reported that age-related neural effects differ in subcomponents of response inhibition as revealed by a hybrid of a Go/Nogo, Simon and a Stop Signal tasks. Thus, ageing does not seem to affect interference control in general, but rather has distinctive effects on different conflict types. However, despite these observations it is difficult to delineate conflict specific neuronal features of ageing, since different conflict types were investigated in independent experimental settings and across independent groups. Kawai et al. (2012) was the first to introduce both Flanker and Simon tasks within one experimental design in young and elderly participants using near-infrared spectroscopy (NIRS). Data from this study revealed that during Flanker task processing elderly participants showed increased activation in the right middle frontal gyrus (MFG) and superior frontal gyrus (SFG). In contrast, during the Simon task the elderly group elicited higher activation over bilateral sites corresponding to SFG. These data again demonstrate that an age-related overrecruitment in frontal brain areas seems depend on different conflict types. However, the NIRS technique only has a restricted spatial resolution of signal origin, and Kawai et al. (2012) only recorded signal in frontal areas.

The aim of the present fMRI study was to investigate whether age-dependent changes in conflict processing differ according to the type of conflict. Therefore, the combined Flanker and SRC task which allows for the separate analysis of S-S and S-R conflicts as well as a combination of both within one experimental setup was conducted by elderly and young participants during fMRI recording. The hypotheses were that 1) elderly show enlarged S-R conflict effects with no increase of conflict effects regarding the Flanker task in elderly, and 2) ageing will differentially affect brain activation patterns in Flanker and SRC task processing.

2.2 Materials and Methods

2.2.1. Participants

Nineteen healthy elderly (10 male; mean age 70.26 years, SD = 3.49) and 20 healthy young (10 male; mean age 22.95 years, SD = 2.72) volunteers participated in the experiment. According to the Edinburgh Handedness Inventory Scale (Oldfield, 1971) all participants were right-handed. No subject reported a history of neurologic or psychiatric disorders. All participants had normal or corrected to normal vision and a comprehensive neuropsychological testing was conducted to exclude participants performing outside age-adjusted norms.

2.2.2. Stimulus material

The experimental setup is described in chapter 1.4.1. There were four experimental conditions: 1) congruent Flanker and SRC condition (FcSc); 2) incongruent Flanker and congruent SRC condition (FiSc); 3) congruent Flanker and incongruent SRC condition (FcSi), and 4) incongruent Flanker and SRC condition (FiSi). 72 trials of each condition were presented in six blocks (each with 60 trials) and separated by short breaks of 10 s. The trial sequence was pseudo-randomized to avoid trial succession effects. Each trial started with a fixation cross presented for 800 ± 150 ms in the center of the screen. The stimulus appeared for 250 ms followed by a blank screen for 2000 ms. The stimulation software Presentation® (Neurobehavioural Systems; https://nbs.neuro-bs.com) was used to display stimuli via a JVC video projector onto a projection screen at the rear end of the fMRI scanner with a viewing distance of about 38 cm.

2.2.3. Image acquisition

A 3-T SIEMENS Magnetom Allegra System (Siemens, Erlangen, Germany) with a T2*-weighted gradient echo-planar imaging (EPI) sequence (28 contiguous slices aligned to AC-PC place, slice thickness 4mm, no gap, TR = 1.5 s, TE = 30 ms, FA = 73°, in-plane resolution 3 mm x 3 mm) and a manufacturer supplied circularly polarized head coil signal was used for functional imaging data acquisition.

2.2.4. Image analysis

Preprocessing and functional data analysis was performed with the Statistical Parametric Mapping software SPM (Version 5; Welcome Department of Cognitive Neurology, London, UK). The first ten volumes of each functional data set were discarded. Scans were re-aligned to the first volume, slice-time corrected and spatially normalized to the standard SPM EPI template in MNI space. Smoothing of the data was conducted using a 8 mm x 8 mm x 10 mm full width at half maximum (FWHM) Gaussian kernel. Data were high-pass filtered (128Hz) to remove low frequency signal drifts. A first-order autoregression model (AR-1) was used to correct temporal autocorrelations.

Regressors were defined by delta functions convolved with a canonical HRF at each stimulus onset. The design matrix consisted of five regressors representing trials with correct responses (FcSc, FiSc, FcSi, FiSi, neutral), an additional regressor for erroneous trials as well as six motion regressors containing movement parameters obtained during realignment.

For the first-level analysis *t*-contrasts were calculated for each participant. Each contrast included a single conflict condition compared to the double congruent condition ([Fisc > FcSc]; [FcSi > FcSc]; [Fisi > FcSc]). Group specific activation was determined with a one sample t-test for each contrast and each group. To investigate age-dependent differences each contrast was entered into a second level analysis using two sample t-tests with the young and elderly participants groups as independent groups. For exploratory purposes an experimental approach with a similar task design introduced by Frühholz and colleagues (2011) was employed. Contrasts were thresholded at $p < .001$ (uncorrected) combined with a cluster extent threshold of $k = 9$. In addition, group contrasts thresholded at $p < .005$ for young and elderly participants respectively were used as an inclusive mask to exclude task irrelevant activation differences. We used the conjunction null hypothesis (Nichols et al., 2005; $p < .005$ (uncorrected), $k = 9$.) for each contrast to identify common activation patterns

2.3. Results

2.3.1 Behavioral data

Reaction times (RT) of correct trials and error rates (ER) were entered into a 2 x 2 x 2 repeated measures ANOVA with the within-group factors *Flanker* and *SRC* and *Age* as a between-group factor. There was a significant main effect for all factors with regard to RTs (Flanker: $F(1,37) = 109.36$, $p < .001$; SRC: $F(1,37) = 49.20$, $p < .001$; Age: $F(1,37) = 21.48$, $p < .001$; see *Figure 3*). In comparison to congruent trials, RTs were slower in incongruent trials with regard to the Flanker conflict (congruent: M = 575 ms, SEM = 14; incongruent: M = 612 ms, SEM=15) and the S-R conflict (congruent: M = 577 ms, SEM = 14; incongruent: M = 610ms, SEM=16) task. Elderly participants presented larger RTs than young controls (young: M = 527 ms, SEM = 20; old: M = 660 ms, SEM=21), and the interaction of *SRC* and *Age* reached significance ($F(1,37) = 6.00$, $p = .019$). Both groups showed larger RTs for the incongruent condition of the SRC task, but the SRC congruency effect was significantly larger in elderly (ΔRT = 45 ms, SEM = 36) compared to young participants (ΔRT = 22ms, SEM = 22; $t(37) = -2.45$, $p = .019$; see Figure 3). There was no *Flanker* x *Group* interaction ($F(1,37) = 1.16$, $p = .288$) or a Flanker x SRC interaction ($F(1,37) = 0.20$, $p = .890$).

For error rates a significant main effect was found for the factors *Flanker* ($F(1,37) = 15.67$, $p < .001$) and SRC ($F(1,37) = 16.23$, $p < .001$). Error rates were higher in incongruent (M = 3.2 %, SEM = 0.75) than in congruent Flanker trials (M = 5.1 %, SEM = 0.74). The incongruent condition (M = 6.2 %, SEM = 1.2) of the SRC elicited higher error rates as compared to the congruent condition (M = 2.1 %, SEM = 0.31, see *Figure 3*). There was no main effect of the factor Age ($F(1,37) = 0.05$, $p = .821$), but the interaction of *Flanker* x *Age* became significant ($F(1,37) = 4.80$, $p = .035$). The difference between incongruent and congruent Flanker trials was significantly higher in young participants (Δerror rates = 3.1 %, SEM = 0.72) in comparison to elderly (Δerror rates = 0.88 %, SEM = 0.68; $t(37) = 2.19$, $p = .035$). There was no significant interaction of *SRC* x *Age* ($F(1,37) = 0.57$, $p = .455$).

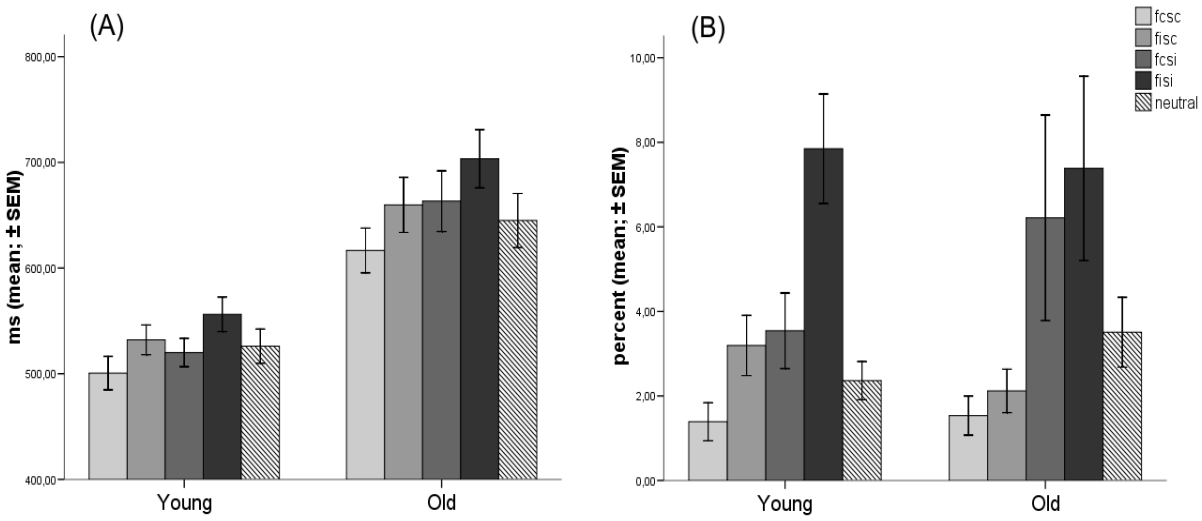

Figure 3 Behavioral data: (A) reaction times and (B) error rates for young and elderly participants. Error bars show the standard error of the mean (SEM).

Taken together, the behavioral data analysis revealed significant effects for both conflict types in both groups with regard to RTs. The congruency effect of the SRC task was significantly larger in elderly participants. Additionally, ERs were modulated by the SRC task in both groups. The Flanker congruency effect for ERs was only evident in young adults.

2.3.2. fMRI data

In a first approach the analysis of the imaging data was based on separately comparing incongruent Flanker [FiSc], incongruent SRC [FcSi], and the double incongruence [FiSi] condition against the double congruence condition [FcSc]. All contrasts were calculated for each group and entered into a between group analysis (see *Table 2* and *Figure 4*).

In young participants the Flanker conflict resolution ([FiSc] > [FcSc]) revealed bilateral activation in the caudate nucleus, in the anterior cingulate gyrus (ACC) and the middle occipital gyrus (MOG) in the right hemisphere. The same contrast in the elderly group elicited signal increases in bilateral occipito-parietal areas including the precuneus (bilateral), the left MOG, the right superior parietal lobule (SPL), the cingulate gyrus , the MFG and the precentral gyrus (PreCG). The data of the conjunction analysis (*Table 3*) showed a bilateral activation pattern in the head of the caudate nucleus during Flanker conflict processing, and group related differences in PreCG and in

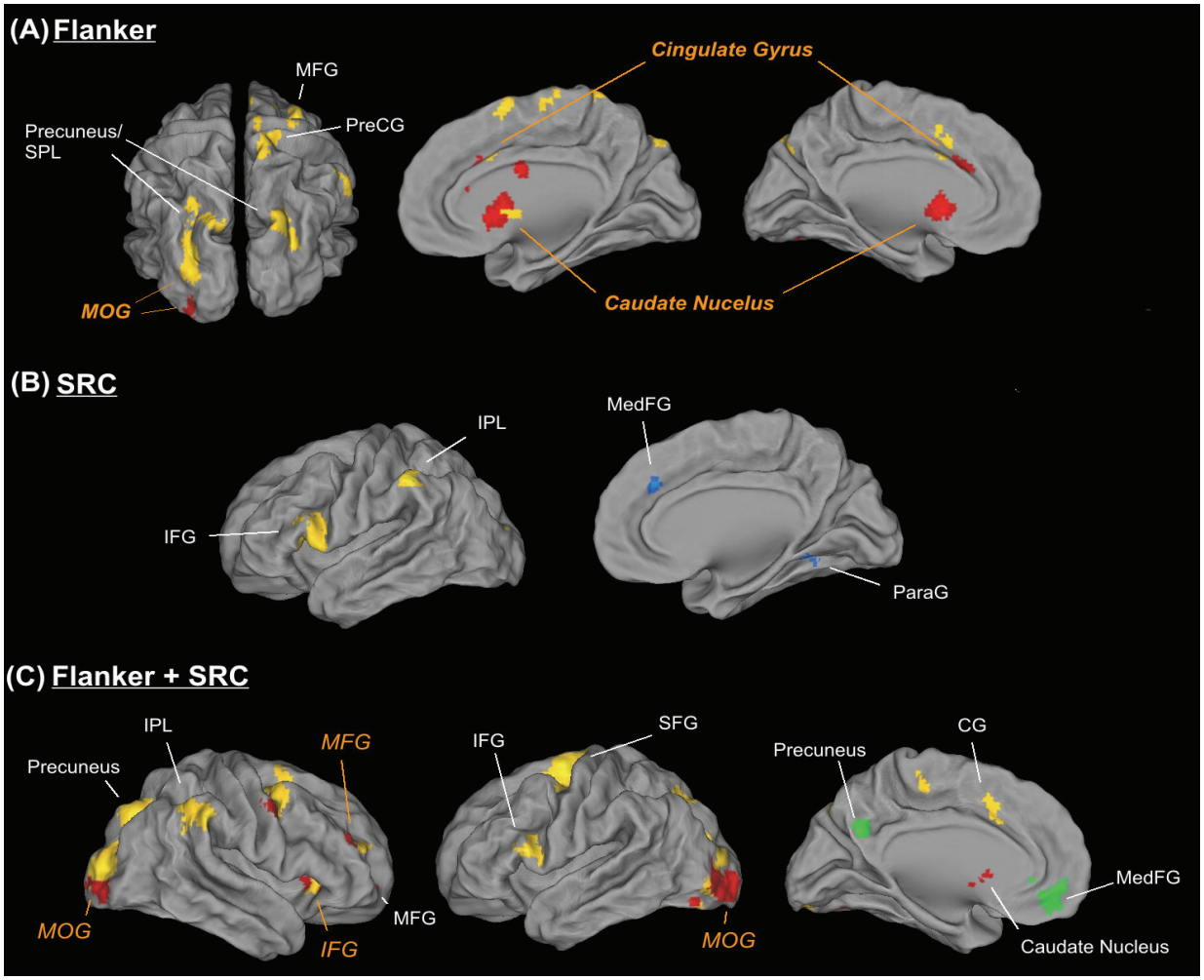

Figure 4 Illustration of different activation patterns for the Flanker (A), the SRC (B), and the double conflict (c) conditions in young and elderly participants. Activation sites of elderly participants are displayed in yellow (activation) and green (deactivation), while active regions of young participants are displayed in red (activation) and blue (deactivation). For the purpose of illustration the threshold was set to $p < .005$ (uncorrected) and k=50.

While in the PreCG Flanker related signal increase was more pronounced in elderly participants, only young participants showed stronger activation in the MOG in response to the Flanker conflict. The analysis of the SRC conflict resolution ([FcSi] > [FcSc]) revealed no significant signal change in the young group. We found various activations for the reverse contrast ([FcSc] > [FcSi]) including the PHG, the IPL, and the medial frontal gyrus (MedFG,). In elderly participants we observed a significant signal increase in the IFG and the IPL (see *Figure 4b*).

There were no significant results in the conjunction analysis of both groups, but a significant interaction in IFG and IPL. Here, SRC related activation only became evident in the elderly subject group.

Table 2 Peak activations for the Flanker [FiSc > FcSc], SRC [FcSi > FcSc], and double conflict (Flanker + SRC) [fisi > fcsc] contrasts, for young and elderly participants. All reported regions are significant at p < .001 (uncorrected) with a spatial extent threshold of k = 9. Abbreviations: x, y, z = MNI coordinates of peak activations.

	Young			Old		
	x y z	t-value	Cluster-size	x y z	t-value	Cluster-size
Flanker Conflict						
Cingulate Gyrus	6 4 29	4.24	12	-2 16 40	4.29	97
Middle Frontal Gyrus				34 4 61	3.95	10
Precentral Gyrus				16 -32 72	4.21	27
Precuneus/				26 -76 42	4.86	89
Superior Parietal Lobule				-24 -80 24	4.71	56
MiddleOccipital Gyrus	-36 -72 -13	4.32	31	-26 -92 16	3.80	10
Caudate	-6 12 0	5.25	138			
	-12 28 0	4.08	11			
SRC						
Inferior Frontal Gyrus				-54 18 8	4.33	22
Medial Frontal Gyrus	10 36 32	-4.11	9			
Inferior Parietal Lobule				-58 -36 48	6.05	35
Superior Temporal Gyrus	48 -38 18	-4.291	12			
Parahippocampal Gyrus	18 -48 -11	-4.45	14			
Flanker Conflict + SRC						
Inferior Frontal Gyrus	34 34 -8	4.34	24	-58 16 16	4.33	25
Middle Frontal Gyrus	30 52 -11	3.95	11	30 6 56	4.82	127
Middle Frontal Gyrus	56 6 42	4.46	15	44 8 45	4.53	30
Superior Frontal Gyrus				-16 14 45	6.20	308
Medial Frontal Gyrus				-2 14 48	3.86	16
Medial Frontal Gyrus				2 -26 56	3.95	22
Medial Frontal Gyrus				2 50 -16	-4.84	112
Anterior Cingulate	12 22 -8	4.16	16			
Precuneus				18 -80 40	4.50	93
Precuneus				-20 -68 48	4.47	24
Precuneus				-6 -60 32	-4.30	15
Inferior Parietal Lobule				66 -30 37	4.11	27
Postcentral Gyrus	32 -38 72	4.25	11			
Middle Temporal Gyrus				-44 -2 -37	-4.56	15
Fusiform Gyrus				-18 -90 -19	3.96	10
MiddleOccipital Gyrus	36 -92 -5	5.4885	67	30 -88 -3	5.23	260
MiddleOccipital Gyrus	-36 -74 -16	4.30	15	-30 -96 16	4.18	44
InferiorOccipital Gyrus	-30 -98 -8	4.91	157			
Caudate	6 12 8	4.13	23			

Table 3 Peak activations derived from a conjunction analysis (intermediate null hypothesis, p < .005 (uncorrected), k = 9) and an interaction analysis (p < .001, uncorrected, k = 9) of the Flanker [fisc > fcsc], SRC [fcsi > fcsc], and double conflict (Flanker + SRC) [fisi > fcsc] contrasts. In addition, group contrasts thresholded at p < .005 for young and elderly participants respectively were used as an inclusive mask. Abbreviations: x, y, z = MNI coordinates of peak activations.

	Conjunction			Interaction		
				Old > Young		
	xyz	t-value	Cluster-size	xyz	t-value	Cluster-size
Flanker Conflict						
Precentral Gyrus				18 -34 72	3.85	12
				Young > Old		
				xyz	t-value	Cluster-size
Middle Occipital Gyrus				-36 -74 -11	3.79	17
Caudate	8 12 5	3.28	57			
	-6 12 0	3.00	12			
				Old > Young		
				xyz	t-value	Cluster-size
SRC						
Inferior Frontal Gyrus				-44 12 21	5.04	60
Inferior Parietal Lobule				-58 -34 48	4.17	21
Flanker Conflict + SRC						
Inferior Frontal Gyrus	34 28 -3	3.13	23			
Medial Frontal Gyrus				-18 12 43	3.99	12
Precuneus	26 -72 37	3.11	10			
Middle Occipital Gyrus	-36 -90 0	3.79	87			
	34 -92 -3	4.69	145			

In the double conflict condition (i.e. trials containing the SRC and the Flanker conflict, [FiSi] > [FcSc]) we found a significant activation comprising a frontal cluster (IFG, MFG and MedFG), posterior (MOG and IOG, PostCG), and subcortical areas (caudate nucleus; see *Figure 4c* and *Table 2*) in young participants. In elderly individuals double conflict trials were associated with a signal increase in IFG, MFG, SFG and the ACC. In addition, we found a significant activation in the precuneus, the IPL, the MOG and the FFG. Deactivations in elderly individuals were found in MedFG, precuneus and middle temporal gyrus. The conjunction analysis for the double conflict condition revealed a common activation cluster in the MOG,

the right IFG and the precuneus. The interaction analysis between both groups showed a significant activation in SFG for elderly participants only.

2.4. Discussion

The aim of the present study was to investigate whether and how ageing affects interference control using different types of conflicts: a Flanker and a SRC conflict as well as a combination of both. The analysis of the behavioral data showed that both young and elderly participants presented Flanker conflict and SRC related effects. RTs were modulated by the Flanker conflict in both groups. Young as well as elderly participants responded significantly faster in congruent compared to incongruent Flanker trials. Error rates in the Flanker task, however, were only increased in young participants. These data correspond to previous studies demonstrating that the Flanker effect does not increase with higher age, and higher accuracy rates in older adults are repeatedly reported in studies using the Flanker task (Wild-Wall et al., 2008; Hsieh and Fang, 2012). These findings may be attributable to different strategies in Flanker task processing. For example, elderly might use a more conservative decision criterion, probably causing to prioritize correct over fast responses (Hsieh and Fang, 2012). For the SRC task performance both groups showed significantly shorter response latencies in the congruent in comparison to the incongruent SRC condition. This effect was larger in elderly than in young participants, and corresponds with various reports in the literature (van der Lubbe and Verleger, 2002; Kawai et al., 2012; Kubo-Kawai and Kawai, 2010).

Flanker Task

The behavioral findings are corroborated by the analysis of the fMRI data which showed that interference resolution in different conflict types rely on distinct neural networks and that ageing has differential effects on conflict processing and their neural correlates. In young adults neuronal activation induced by the Flanker conflict was found in a network comprising MOG, ACC and caudate nucleus. In elderly participants, Flanker incongruent trials elicited activation in MOG, precuneus, cingulate gyrus, MFG and PreCG. Although both groups showed increased activation in MOG and cingulate gyrus there was no direct overlap of the activated clusters. A conjunction analysis revealed common bilateral activation in the caudate nucleus.

However, the caudate activation in the group contrast of the elderly participants only became evident when lowering the threshold to $p < .002$. These findings indicate that the older and younger participants partly share similar mechanisms of Flanker conflict processing. Comparable activation patterns in young and elderly individuals during conflict resolution have also been reported in previous studies introducing the Stroop and the Flanker tasks (Zysset, 2006; Langenecker, 2004; Zhu, 2010). These data suggest a "core network" comprising cingulate cortex and basal ganglia activation underlying cognitive control processes in the respective subgroups. Within the framework of conflict processing theories the cingulate cortex is associated with evaluative functions such as conflict detection and task monitoring (Carter et al., 1998; van Veen and Carter, 2002; Kiehl et al., 2000) and/or response selection (Liu et al., 2004). The basal ganglia also seem to play a role in cognitive control processing. Besides clinical data that showed impaired decision making, task switching and flexibility in patients with basal ganglia dysfunctions (e.g. Parkinson's (Mimura et al., 2006; Brand et al., 2005; Cools et al. 2001; Brown and Marsden, 1990) or Huntington's disease (Hanes et al. 1995; Aron et al., 2003b)) there is also evidence from neuroimaging studies including healthy participants demonstrating that the basal ganglia are also consistently found to be involved in tasks, which demand high cognitive control during decision making (Forstmann et al., 2008; Tanaka et al., 2004). In particular, the caudate nucleus seems to play a critical role in adjusting the decision criteria (Kuchinke et al., 2011; Forstmann et al., 2008). Thus, the caudate nucleus activation in resolving incongruent Flanker trials might reflect the participants' adjustment of the response thresholds in order to avoid response activation triggered by the irrelevant input channel.

Besides the aforementioned common activation pattern, there were also significant differences between groups. An interaction analysis revealed that elderly showed additional activation in PreCG, while young participants additionally recruited a posterior cluster comprising IOG and MOG. In addition, within-group comparisons showed an increased MFG and precuneus activation in elderly participants only. This recruitment of additional brain areas in elderly participants was also shown in previous studies of conflict control (Langenecker et al., 2004; Zysset et al., 2006). We suppose this additional fronto-parietal activation patterns in older participants to reflect compensatory control mechanisms such as increased efforts in spatial attention and top-down attentional control or additionally updating task set information to optimize performance (e.g the precuneus activation, see Jahn et al., 2011).

SRC Task

In contrast to the Flanker conflict incongruent SRC trials were mainly associated with a signal decrease in the IPL, the MedFG, and the PHG in young participants. A lack of signal increase in young participants during the processing of incongruent SRC trials was also found by Lee et al. (2006). Furthermore, a previous study from our own group using a similar double conflict task design (Frühholz et al., 2011) also yielded deactivations in incongruent SRC trials in young adults. These data may indicate that young participants benefit from corresponding spatial information as found in double congruence trials and thus might rather reflect a facilitation than an interference effect. This hypothesis is corroborated by previous studies showing medial frontal areas involved in facilitatory effects in conflict tasks. Swick and Jovanovic (2002) presented a case study in which a patient with a lesion in the mid caudal area of the ACC showed a lack of facilitation in a Stroop task when compared to healthy controls. Furthermore, activation in several regions of the medial frontal wall was also demonstrated during congruent Stroop trials in a positron emission tomographic study with healthy adults (Carter et al., 1995). Further active clusters in the PHG and the IPL might represent an enhanced processing of visual characteristics (shape) of the arrows that are transferred into spatial cues (Bar et al., 2001; Spiridon and Kanwisher, 2002). On the other hand, elderly participants showed increased activation in IFG and IPL during incongruent SRC trials. The IFG plays a substantial role in implementing inhibitory control and is frequently recruited during the processing of conflict tasks (Aron et al., 2003a; Hampshire et al., 2010; Chikazoe et al., 2007). In addition, age-dependent activity increase was found in the IFG in a Stroop task (Zysset et al., 2006; Langenecker et al., 2004). The IPL is usually associated with processing of visuo-spatial information and attentional top-down control. Thus, the fronto-parietal activation patterns in elderly participants might reflect additional demands of inhibitory control and attentional resources to resolve the SRC task.

In contrast to the Flanker task, there were no common activation patterns in young and elderly adults while resolving the SRC task. This finding may indicate that both groups make use of different strategies when irrelevant information interferes with correct response selection. While younger participants seem to also consider irrelevant information for response selection, elderly participants show an activation pattern that is typically associated with inhibition control. The present finding of neuronal activation in the SRC task does not confirm studies of interference control in ageing that found similar neural substrates of inhibition in both age groups (Zysset et al., 2006; Langenecker et al., 2004; Zhu et al., 2010). The present behavioral

and imaging data rather indicate that SRC is processed qualitatively different in elderly and younger individuals.

Double Conflict condition

In young participants, trials demanding the simultaneous resolution of two different types of conflicts elicited activation of a network comprising MOG, caudate nucleus, IFG, and MFG. This pattern shares similarities with the activation found in the single Flanker condition, but extends to the ventrolateral prefrontal (BA 47) and the orbitofrontal cortex (BA 11). This finding corroborates the fMRI data of previous studies of our group where we introduced double conflict paradigms in young adults . Although the type of conflicts differed between studies we found a distinctive activation pattern for the double conflict conditions in the MFG (Wittfoth et al., 2009) and in the frontopolar cortex (Frühholz et al, 2011). Thus, the additional recruitment of middle and inferior frontal areas during monitoring of simultaneously presented conflict types in the present study might indicate the implementation of superordinate control mechanisms that regulate the processing of higher conflict situations. Elderly participants showed stronger activations and a more extended neural network during double conflict trials comprising MOG, precuneus, MFG and ACC (comparable to the single Flanker condition) and additional activations in the left IPL and the IFG (as also found in the single SRC condition). The conjunction analysis demonstrated a network of brain areas, which is recruited by both groups during double conflict trials comprising bilateral MOG and right IFG and precuneus. The additional frontal medial wall activity in elderly participants as demonstrated by an interaction analysis might be attributable to the generally higher task demand of double conflict trials due to the higher amount of interference.

In conclusion, these findings suggest that elderly and young participants use similar networks to resolve interference from two concurrent conflicts, which however seem to be more pronounced and leading to an additional recruitment of MedFG in the elderly.

Ageing effects on different conflict types

Taken together, these data corroborate the hypothesis that different components of interference control evolve differently with advanced age. While the core neural mechanisms underlying S-

S conflict resolution remain stable, neural processing of S-R conflicts is substantially altered in elder participants. Turner and Spreng (2012) demonstrated that different types of executive functions, such as working memory and inhibition, show distinctive neural age-related effects. Though they provide no information about how different components of interference control develop with increasing age, this review clearly demonstrates that ageing does not have a unitary effect on different executive functions. Another recent study (Sebastian et al., 2013) comprising a Go/Nogo, a Simon and a Stop Signal task confirmed that differential ageing effects are also found in different components of inhibition. While the Go/NoGo and Simon tasks showed an increased neural activation in prefrontal areas in elderly participants, a decrease of neural activity was found during the Stop Signal task in the same group. Our findings are also in line with the study of Kawai et al. (2012) analyzing the neural processing of Flanker and Simon conflicts in young and elderly participants using NIRS. In this study, the pattern of age-dependent neural effects differed between both conflict tasks. Elderly participants showed increased bilateral activation in the SFG in the Simon task, while Flanker task was associated with increased activation in the right MFG and SFG.

Several studies clearly demonstrate that ageing goes along with deficiencies in the inhibition of distractors, while neural mechanisms related to the processing of the target stimulus largely remain intact (de Fockert et al., 2009; West and Alain, 2000; Wascher et al., 2012). As both the S-S and S-R conflicts require the inhibition of distracting information, the inhibition of SRC task-related distractors is particularly vulnerable to age-related alterations. Wild-Wall and colleagues (2008) report electrophysiological markers reflecting the processing of the target stimulus in a Flanker task to be enhanced in elderly participants. They also found lower error rates in elderly compared to young participants and argued that elderly participants show a stronger attentional focus on the target stimulus to reduce interference induced by the Flanker stimuli. A similar strategy might have also been employed by the elderly participants in the present study. The smaller Flanker effect in the error rates of elderly participants supports the hypothesis that elderly focus on the target stimulus and thus lower the processing of flanking distractors. Furthermore, additional activation of frontal and parietal areas in elderly in the incongruent Flanker condition might indicate additional top-down regulation that amplifies relevant (target) and attenuates irrelevant (flanker) input channels. However, this strategy does not promote interference reduction for SRC-related distractors since they are confounded with the target stimulus (Proctor et al., 2005). In contrast, an enhanced processing of the target stimulus might lead to a concomitant deeper processing of SRC-related distractors and thus stronger SRC induced interference. Elderly participants presumably do not employ a

compensatory strategy to reduce interference resulting from SRC distractors. Thus, the recruitment of IFG and IPL seem to reflect these additional demands for conflict resolution. In conclusion, the present data demonstrate that ageing generally does not impair conflict resolution, but differentially interferes with different subcomponents of conflict processing.

3. Experiment 2

3.1. Introduction

Various studies indicate that interference control is not a unitary function but rather consists of different subcomponents, that are associated with distinct spatial and temporal characteristics of neural processing (Egner et al., 2007; Frühholz et al., 2011; Nee et al, 2007). Furthermore, there is evidence that ageing does not affect all subcomponents and subprocesses of interference resolution in the same way and in the same amount but rather shows effects that are specific for different conflict types (Kawai et al., 2012; Sebastian et al., 2013). Increased reaction time and error rate effects in elderly individuals are frequently reported in studies using SRC task (Kubo-Kawai and Kawai, 2010; van der Lubbe and Verleger, 2002), while in many experiments employing the Flanker task no significant differences between young and old adults are found (Falkenstein et al., 2002; Nieuwenhuis et al., 2002). These differences can also be documented when both types of conflicts are investigated within the same experiment (Kawai et al., 2012). Experiment 1 (see previous chapter) demonstrated that the differential effects of ageing on the SCR and Flanker conflict tasks are also reflected in different neural activation patterns: Elderly adults presented a more widespread activation pattern when compared to their younger peers in response to the Flanker conflict. However, both groups also recruited similar brain regions such as caudate nucleus and prefrontal brain areas. In contrast, the SRC task elicited substantially different activation patterns in both groups: while elderly individuals showed activation in frontal and parietal areas, young adults mainly exhibited a deactivation pattern. These markedly different activation patterns suggest qualitative age-related differences in the processing of SRC between young and elderly individuals. These data strongly suggest that different conflict types are processed in distinctive neural networks and additionally show that these networks are differentially affected by ageing.

The specificity of ageing effects on different conflict types raises the question whether ageing elicits distinctive effects on different temporal stages of conflict processing as well. Various studies found that the resolution of different conflict types is not only linked to dissociable neural activation patterns but also to distinct temporal processing stages (Frühholz et al., 2011; Li et al.; 2014; Wang et al., 2014). The present study therefore aims at investigating the effects of ageing on different stages of conflict processing using ERPs that are known to be involved in conflict resolution such as the N2 and P3. The N2 is a negative deflection occurring 250-300 ms after stimulus onset. It can be subdivided to different subcomponents depending on the

topography and the presumed underlying cognitive processes (for review see Folstein and Van Petten, 2008). Conflict tasks as well as other task conditions that require response inhibition modulate an N2 subcomponent that appears over frontal electrodes. The amplitude of the anterior N2 is enhanced in conditions with an increased demand for inhibition such as incongruent Flanker and Simon task trials (Melara et al., 2008; Van't Ent, 2002), a finding that might indicate an N2 involvement in response inhibition and conflict monitoring. This hypothesis is furthermore substantiated by source analysis studies that reported neural generators of the N2 in the medial wall of the frontal cortex (Bekker et al., 2005; Wascher et al., 2011), a region frequently activated in monitoring tasks and response selection (Carter et al., 1998).

The N2 component seems to be affected by increasing age. A delay of N2 latency (Falkenstein et al., 2002) and a significant decrease of amplitude of the N2 in elderly subjects have been reported across different tasks (Bertoli and Probst, 2005; Czigler, 1996; Lucci et al., 2013; Wascher et al., 2011). In accordance with these findings, Wild-Wall and colleagues (2008) also reported that elderly exhibit a diminished N2 amplitude in a Flanker task The authors argued that this age effect possibly reflects an altered processing strategy in elderly that reduces the interference triggered by incongruent Flanker stimuli. Whether Flanker conflict and SRC processing show different modulations of the N2 component or whether ageing has conflict specific effects on the N2 is still unclear. However, there is evidence that ageing does not generally affect the N2 component but rather shows specific effects for different processing contexts (Falkenstein et al., 1995).

The later P3 component is also reported to be influenced by different conflict tasks. Comparable with the N2, the P3 can be subdivided in different subcomponents with different topographies, reflecting different cognitive processes. The parietal P3b component seems to be related to the allocation of attentional resources (Polich and Heine, 1996) and might additionally indicate the timing of stimulus evaluation (Duncan-Johnson, 1981; Kutas et al., 1977). The P3b amplitude and latency are modulated by both the Flanker and the Simon task (Frühholz et al., 2011; Umebayashi and Okita, 2010; Van't Ent, 2002). The effects of ageing on the P3 component are characterized by a decrease of amplitude and a delay of latency (Dujardin et al., 1993; Polich, 1996). This effect was also illustrated in the context of conflict processing (Van der Lubbe and Verleger, 2002; Wild-Wall et al., 2008). In contrast to the N2 Falkenstein et al. (1995) reported the P3 component to be equally affected by ageing in different stimulation contexts. The authors argued that cognitive processes indexed by the P3

might be less specific to different components of inhibition in comparison to the N2 component.

Another component that is influenced by conflict processing is the P2 component. Gajewski et al. (2008) reported the P2 amplitude to be increased in incompatible stimulus conditions. West and colleagues (2004) additionally found that in a numerical conflict task, stimulus incongruence elicited an increase of the P2 amplitude. The amplitude enhancement in trials with incongruent stimuli possibly reflects higher demands on stimulus evaluation (Gajewski et al., 2008; Potts, 2004). There is sparse literature on how ageing affects the P2 component in the context of conflict processing. However, age-related changes of the P2 component were demonstrated in a spatial working memory task (McEvoy et al.; 2001). In this study elderly individuals elicited an enhancement of the P2 amplitude in comparison to young adults, while P2 latency remained unchanged. Furthermore, the age-related enhancement of the P2 amplitude in a Stroop task (West and Alain, 2000) clearly demonstrates that this component is of great relevance when investigating ageing effects on interference control processing.

The aim of the present study was to investigate whether ageing affects specific stages of conflict processing in different conflict task conditions. Therefore, elderly adults and young controls underwent EEG recording with a combined SRC and Flanker conflict task. In consideration of previous results, it was hypothesized that ageing differentially affects the P2, N2, and P3 components of information processing.

3.2. Methods

3.2.1. Participants

Twenty young and 25 elderly subjects participated in the present study. One male participant in each group had to be excluded from further analysis due to massive movement artifacts in EEG data. Additionally, a comprehensive neuropsychological examination revealed minor cognitive deficits in one male elderly participant, who was also excluded from further analysis. Thus, the final study sample consists of 19 young (10 male, mean age 23.05 years, SD= 2.76) and 23 elderly adults (11 male, mean age 70.32 years, SD = 3.24). All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1970), had normal or corrected to normal vision, and reported no prior history of psychiatric or neurological disorders.

3.2.2. Stimulus material

The task design is described in chapter 1.4.1. The four experimental conditions (congruent Flanker and SRC condition (FcSc); incongruent Flanker and congruent SRC condition (FiSc); congruent Flanker and incongruent SRC condition (FcSi), and incongruent Flanker and SRC condition (FiSi)) were presented in six blocks of 60 trials separated by short breaks of 10 seconds. There were 72 trials of each condition. Trial sequence was pseudo-randomized to avoid effects of trial succession. Each trial started with a white fixation cross on black background in the center of the screen (800 ± 150 ms). Thereafter, the set of arrows appeared for 250 ms followed by a blank screen for 2000 ms. Stimuli were presented on a computer screen (refresh rate 60 Hz) using Presentation Software (neurobehavioral Systems; https://nbs.neuro-bs.com). Participants were seated in front of the screen with a viewing distance of 60 cm. The experiment was conducted in a darkened room.

3.2.3. EEG recording

EEG signal was recorded using 64 Ag-AgCl electrodes placed on an elastic cap according to the 10-10-system with a sampling rate of 512 Hz. Interconnected ear lobe electrodes were used as reference. EEG signal was amplified by a REFA® multi-channel system (TMS International; www.tmsi.com), and impedance threshold was set to 10 kΩ. Eye movements and blinks were monitored by vertical and horizontal electrooculograms. Offline data processing was performed with the Brain Electrical Source Analysis software (BESA®, Version 5.1.8.10, MEGIS Software GmbH, Gräfelf ng, Germany), and comprised band-pass filtering (0.1-20 Hz) and rereferencing to average reference. Trials were averaged stimulus-locked within a time frame of 100 ms before and 800 ms after stimulus onset. EOG artifacts were corrected using the algorithm introduced by Ille et al. (2002). Each trial was visually inspected, and incorrect trials and trials with artifact contamination were discarded from further analysis. To avoid differences of trial number between conditions and groups 50 (±10) trials equally distributed over the six runs were included in the EEG data analysis.

2.2.4. ERP analysis

According to the hypotheses data analyses focused on the P2, N2, and P3 ERP components. The respective time windows for the P2 (140-220 ms), N2 (240-330 ms) and P3 (300-580 ms) components were determined by visual inspection of the grand average waveforms of both groups. Analyses included peak amplitude and latency in contrast to mean amplitude to avoid the problem of different onsets and durations of the ERP components between young and elderly participants. Individual peak amplitudes and latencies were determined and entered into a 3 x 3 x 2 x 2 x 2 ANOVA with *Frontality* and *Laterality* of electrode position, *Flanker* (congruent vs. incongruent) and *SRC* (congruent vs. incongruent) conditions as within-subject factors, and *Age* (young vs. elderly) as between-subject factor. Due to different scalp distributions of the P2, N2 and P3 components, different electrode positions were chosen for the factors *Frontality* and *Laterality* for the different time windows. EEG data show that P2 and N2 are especially pronounced over fronto-central electrodes in both groups (see *Figure 8)*. Thus, fronto-central electrodes (C1, Cz, C2; Fc1, Fcz, Fc2; F1, Fz, F2) were used for the ANOVA of the P2 and the N2 component. For these components the factor *Frontality* consisted of the electrode positions C, Fc, and F while the factor *Laterality* comprised electrode positions on the left (1) and right (2) side and on the scalp midline (z). In contrast, the P3 manifests over centro-parietal recording sites in young and elderly (see *Figure 2*). The peak amplitudes and latencies from the electrode postions C1, Cz, C2, Cp1, Cpz, Cp2, P1, Pz and P2 were included in the P3 analysis. For the P3 analysis the levels of the factor *Frontality* referred to parietal (P), centro-parietal (CP) and central (C) recording sites. The factor *Laterality* comprised the levels left (1) vs. right (2) vs. midline (z) electrode position. The Greenhouse-Geisser correction was applied for violations of sphericity. LSD (least significant difference) post-hoc t-tests with a significance level of $\alpha = 0.05$ were conducted to compare the levels of the respective main factors. Post-hoc Student's t-tests were used to examine significant factor interaction ($\alpha = 0.05$).

3.3. Results

3.3.1. Behavioral data

Reaction times (RT) and error rates were each entered into a 2 x 2 x 2 ANOVA with the within-subject factors *Flanker* (congruent vs. incongruent) and *SRC* (congruent vs. incongruent), and the between-subject factor *Age* (young vs. elderly). *Figure 5* shows RTs and error rates for both groups and all conflict conditions. The RT analysis revealed a significant main effect for the factors *Flanker* ($F(1,40) = 102.66$, $p < .001$) and *SRC* ($F(1,40) = 79.51$, $p < .001$). Both conflict types elicited longer reaction times in incongruent (Flanker: M = 555.50 ms; SEM = 14.32; SRC: M = 553.71 ms; SEM = 13.76) compared to congruent trials (Flanker: M = 516.31 ms; SEM = 13.22; SRC: M = 518.10 ms; SEM = 13.81). The factor *Age* was also significant ($F(1,40) = 14.04$, $p < .001$). RTs were increased in elderly (M = 587.05 ms; SEM = 18.36) compared to young adults (M = 484.76 ms; SEM = 20.20). Additionally, the interaction of *Flanker* x *SRC* survived the significance threshold ($F(1,40) = 4.73$, $p = .036$). There was a significantly increased RT difference between congruent and incongruent trials, when two sources of conflict were present ($\Delta M = 9.95$ ms; $p = .030$).

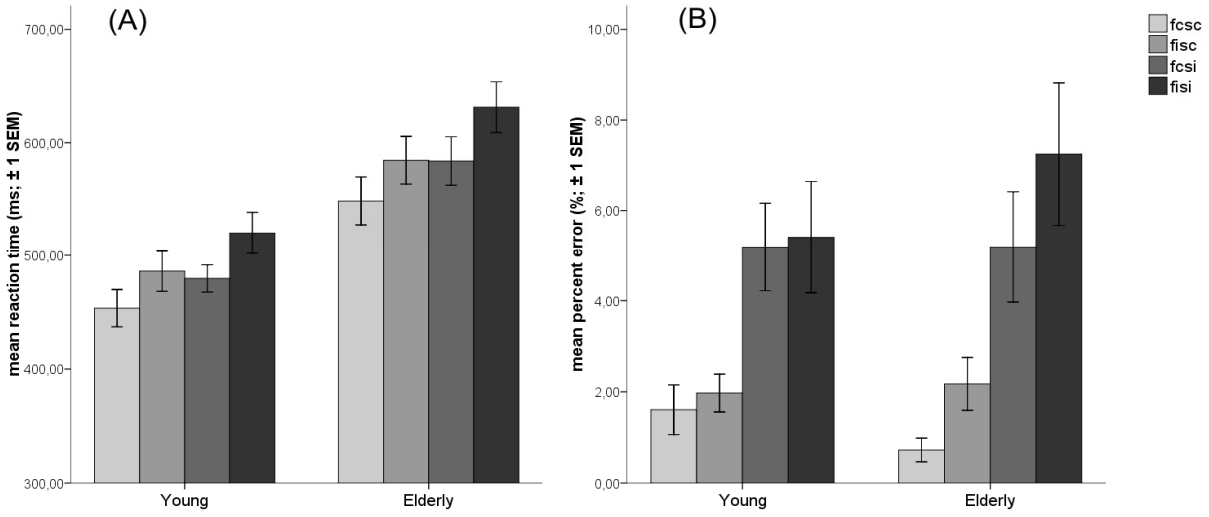

Figure 5 Behavioral performance of young and elderly participants for the conditions fcsc (both Flanker and SRC congruent), fisc (Flanker incongruent, SRC congruent), fcsi (Flanker congruent, SRC incongruent), and fisi (both Flanker and SRC incongruent). Error bars show standard error of mean.

There were also significant main effects for the factor *SRC* ($F(1,40) = 25.81$, $p < .001$) but not for the factor *Flanker* ($F(1,40) = 4.02$, $p = .052$) regarding the error rates (see *Figure 5*). All

participants made more errors in incongruent SRC trials when compared to congruent SRC and Flanker trials. There was no significant group effect or interactions for error rates ($F(1,40) < 1$).

In contrast to the analysis of RTs of the fMRI session (Experiment 1, see previous chapter), there was no significant interaction of *Age* x *SRC* in the present RT data, indicating that the SRC related RT effect is not increased in advanced age during EEG recording. These inconsistencies are possibly rooted in the general RT delay during fMRI recording that is found across different studies with different task designs. Indeed, the comparison of the mean RTs of the EEG and the fMRI session (reported in the present and previous experiment) yielded a significant response delay during fMRI recording in young (EEG: M = 491 ms: SEM = 15.02; fMRI: M = 535 ms: SEM = 14.88; $p = .012$) and elderly participants (EEG: M = 595 ms: SEM = 24.34; fMRI: M = 661 ms: SEM = 25.29; $p < .001$). Various studies showed that the SRC effect size varies in dependence of response speed (De Jong et al., 1994; Frühholz et al., 2011; Juncos-Rabadán et al., 2008). Importantly, this interdependence is distinctive for different age groups leading to different group effects in slow vs. fast reactions (Juncos-Rabadán et al., 2008; Castel et al., 2007). Hence, the age-specific interdependence of response speed and SRC effect possibly manifests differentially in the EEG and fMRI related behavioral data and thus accounts for the inconsistent results. Thus, a post-hoc analysis of the SRC and Flanker conflict effect for different RT quartiles for both groups and session types was conducted. The results are illustrated in *Figure 6* (SRC) and *Figure 7* (Flanker conflict).

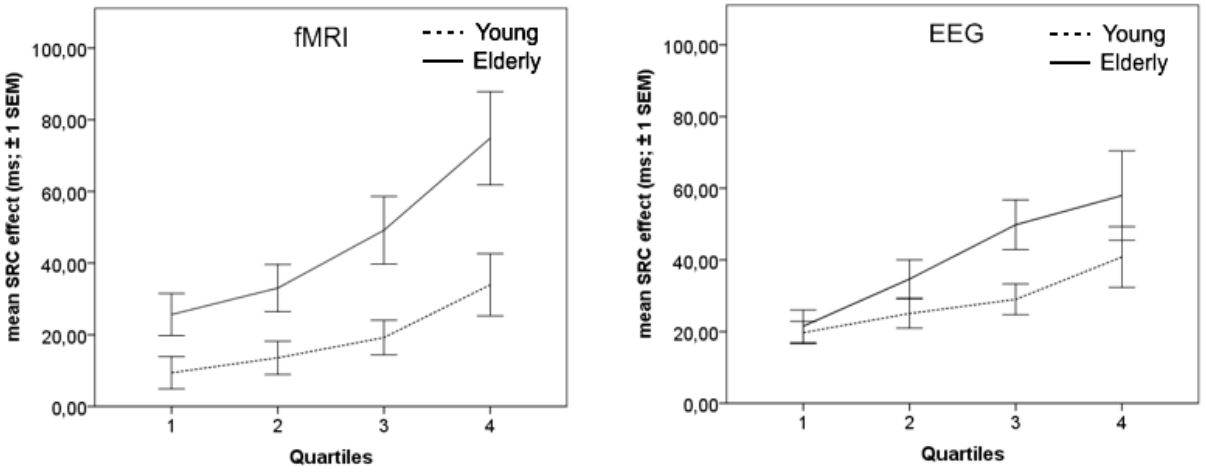

Figure 6 SRC effect (SRC incongruent - SRC congruent) for the different reaction time quartiles during EEG and fMRI recording.

A two-sample t-test revealed that the Flanker effect did not significantly differ between elderly and young adults for all RT quartiles in the EEG (quartile 1: $p = .947$: quartile 2: $p = .562$;

quartile 3: p = .600; quartile 4: p = .717) and the fMRI session (quartile 1: p = .438 quartile 2: p = .835; quartile 3: p = .283; quartile 4: p = .263). In contrast, the SRC related RT effect was increased in elderly in every quartile of the RT data of the fMRI session (quartile 1: p = .034 quartile 2: p = .020; quartile 3: p = .007; quartile 4: p = .012). Importantly, there was also a significant group difference of the SRC effect in the third quartile of the RT data obtained in the EEG session (quartile 1: p = .756 quartile 2: p = .175; quartile 3: p = .020; quartile 4: p = .282). These results show that the age-related increase of the SRC effect is not evident in very fast responses but rather manifests with slower RTs.

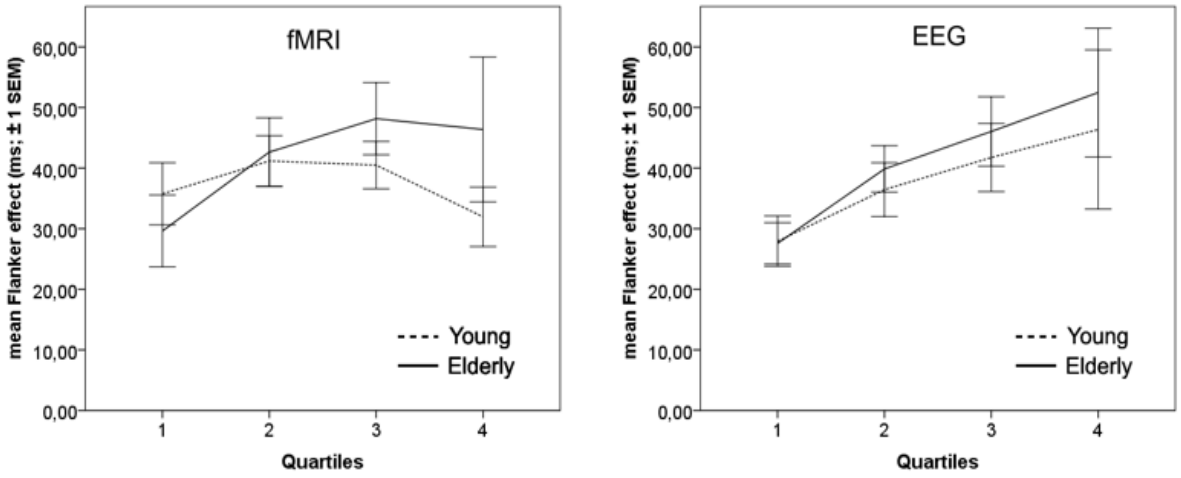

Figure 7 Flanker conflict effect (Flanker incongruent- Flanker congruent) for the different reaction time quartiles during EEG and fMRI recording. Error bars show the standard error of the mean (SEM).

3.3.2. ERP data

Grand averages and scalp topography of P2, N2 and P3 are shown *in Figure 8. Figure 8a* displays the grand average waveforms for young and elderly adults over parietal, central and frontal electrodes. *Figure 8b* demonstrates the scalp topography for three time points referring to the P2, N2, and P3 components. The topography of the P2 component is characterized by a peak amplitude over frontal electrodes in both groups. The N2 also has a frontal orientation in young individuals. In elderly the N2 is located more posteriorly over central electrodes. The P3 has a parietal orientation in young and elderly participants.

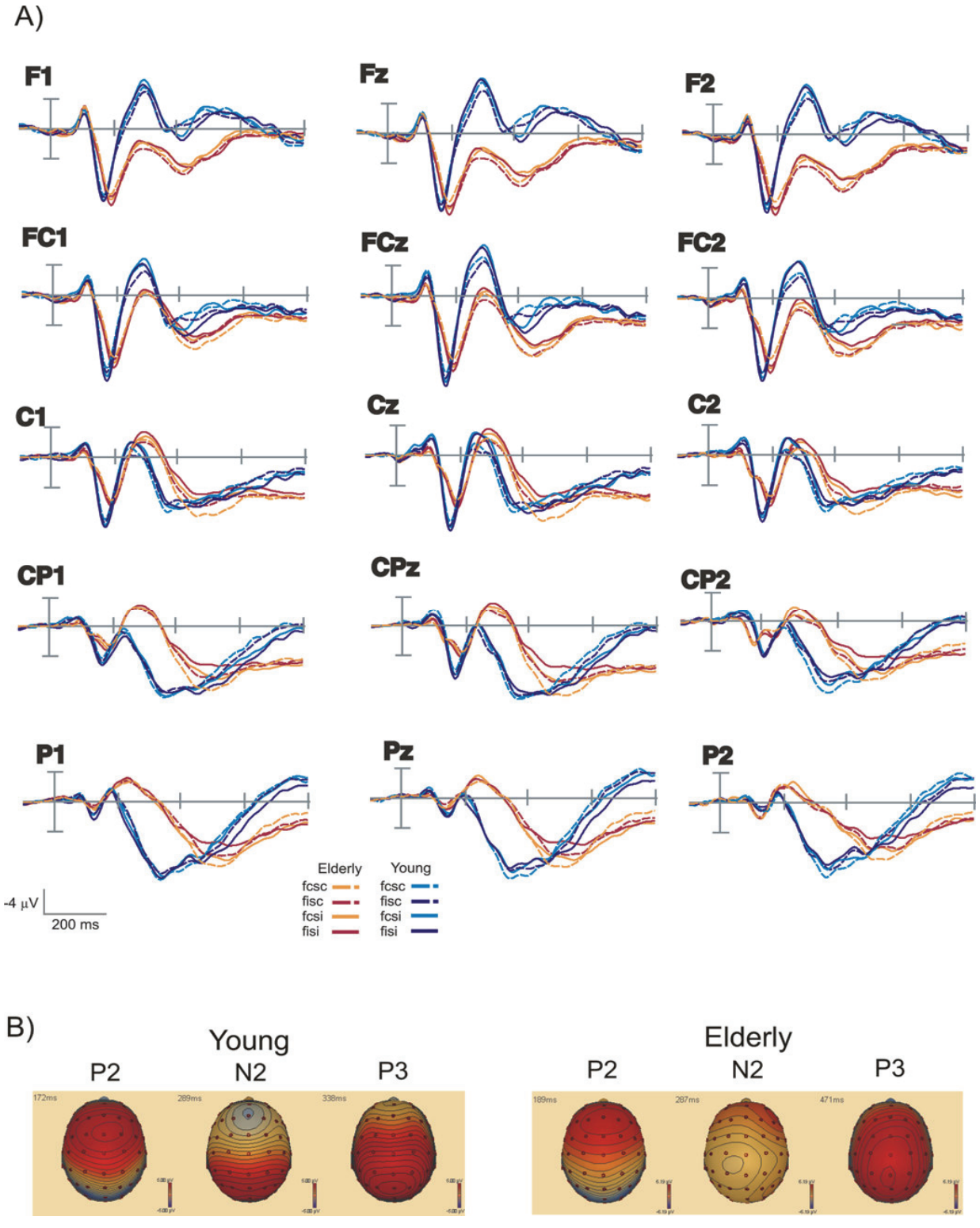

Figure 8 A) Group-averaged event-related potentials for the conditions FcSc (Flanker and SRC congruent), FiSc (Flanker incongruent, SRC congruent), FcSi (Flanker congruent, SRC incongruent) and FiSi (Flanker and SRC incongruent) for young and elderly adults. Stimulus onset is shown by the vertical line. Ticks on the time axis represent 200 ms. B) Topography of the P2, N2, and P3 component for young and elderly participants.

3.3.2.1. P2

Statistical analysis of the P2 time window revealed a significant main effect for the factor *Flanker* ($F(1,40) = 24.17$, $p < .001$) with increased amplitudes in incongruent ($M = 5.28$ µV; $SEM = 0.32$) compared to congruent ($M = 4.87$ µV; $SEM = 0.32$) Flanker trials. The factor *Frontality* also elicited a significant main effect ($F(2,39) = 19.09$, $p < .001$) with higher amplitudes over frontal ($M = 5.48$ µV; $SEM = 0.37$) and frontocentral ($M = 5.51$ µV; $SEM = 0.35$) than central ($M = 4.24$ µV; $SEM = 0.31$) electrodes. In contrast, there were no significant main effects for the factor *SRC* ($F(1,40) = 1.36$), *Laterality* ($F(2,39) = 2.35$) and *Age* ($F(1,40) < 1$). The interaction of *Laterality* x *SRC* x *Age* was significant ($F(2,39) = 4.44$; $p = .015$; see *Figure 9*). In contrast to the younger participants (congruent: $M = 5.19$ µV; $SEM = 0.46$; incongruent: $M = 5.07$ µV; $SEM = 0.46$; $p = .315$) the comparison of the congruent ($M = 4.78$ µV; $SEM = 0.42$) and incongruent ($M = 5.02$ µV; $SEM = 0.42$) SRC condition reached significance ($p = .016$) in elderly subjects over right electrode positions (F2, Fc2, C2). The interaction of *Frontality* x *Flanker* was also significant ($F(2,39) = 4.43$; $p = .015$) due to an increased Flanker effect over frontocentral ($\Delta M = 0.50$ µV; $SEM = 0.09$) compared to central ($\Delta M = 0.25$ µV; $SEM = 0.96$) electrodes ($p < .001$). With respect to the P2 latency a significant main effect was only found for the factor *Age* ($F(1,40) = 24.37$, $p < .001$). The peak latency of the P2 was shorter in young ($M = 172.15$ ms; $SEM = 2.68$) participants than elderly adults ($M = 189.99$ ms; $SEM = 2.43$). Further main effects or interactions did not reach significant (all $Fs < 3.12$ all $ps > .066$).

3.3.2.2. N2

The analysis of the N2 amplitude revealed a significant main effect for the factors *Flanker* ($F(1,40) = 31.49$, $p < .001$), *Laterality* ($F(2,39) = 12.04$, $p < .001$), and *Age* ($F(1,40) = 11.62$, $p = .002$). The amplitude of the N2 component was significantly more negative in trials with incongruent ($M = -1.96$ µV; $SEM = 0.33$) than congruent Flankers ($M = -1.38$ µV; $SEM = 0.35$). Furthermore, the N2 amplitude in elderly ($M = -0.51$ µV; $SEM = 0.45$) was not as pronounced as in young adults ($M = -2.83$ µV; $SEM = 0.45$). The N2 amplitude was more negative over central electrodes ($M = -1.97$ µV; $SEM = 0.37$) and left ($M = -1.72$ µV; $SEM = 0.34$) electrodes compared to right electrodes ($M = -1.32$ µV; $SEM = 0.33$; $p < .001$; $p = .019$). The factors *Frontality* ($F(2,39) = 1.20$, $p = .305$) and *SRC* ($F(1,40) < 1$, $p = .348$) did not reach

significance. There was an interaction of *Frontality x Age* ($F(2,39) = 29.71$, $p < .001$) based on a significant amplitude difference between frontal and frontocentral electrodes that was detectable only in elderly individuals (frontal: M = 0.86 µV; SEM = 0.52; frontocentral: M = -0.51 µV; SEM = 0.50; $p < .001$) and not in young (frontal: M = -3.65 µV; SEM = 0.72; frontocentral: M = -3.15 µV; SEM = 0.57; $p = .088$). In addition, there was a significant interaction of *Laterality* x *Flanker* x *Age* ($F(2,39) = 3.91$; $p = .024$) due to an increased Flanker effect in young (ΔM = -0.85 µV; SEM = 0.20) compared to elderly subjects (ΔM = -0.36 µV; SEM = 0.11; $p = .046$) over right electrodes (F2, Fc2, C2).

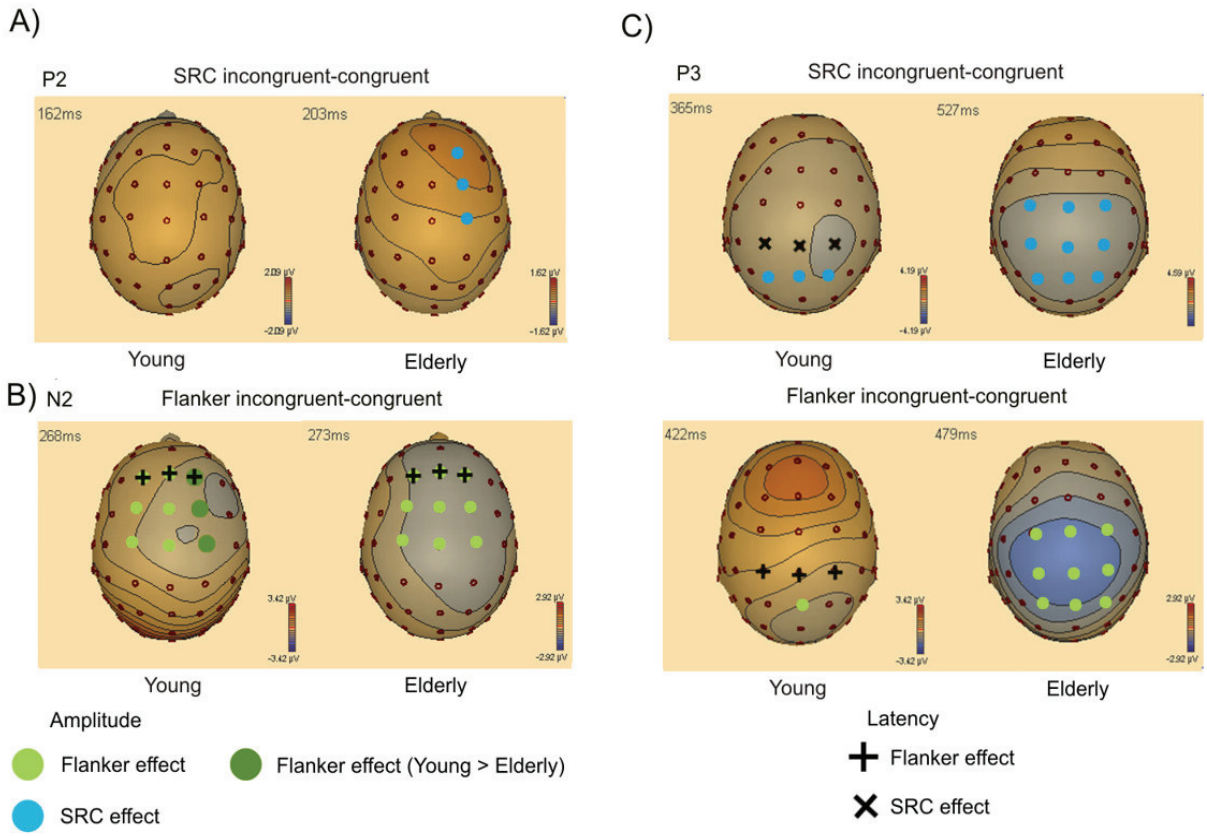

Figure 9 A) Topography of amplitude difference between SRC incongruent – congruent condition for the P2 component (140-220 ms). Blue circles indicate electrodes with a significant SRC amplitude effect. B) Topography of amplitude difference between Flanker incongruent – congruent condition for the N2 component (240-330 ms). Light green circles represent electrodes with significant Flanker conflict amplitude effect. Dark green circles indicate, that this amplitude effect was larger in young compared to elderly adults. Black crosses represent electrodes with significant Flanker conflict induced latency effect. C) Topography of amplitude difference between SRC and Flanker incongruent – congruent condition for the P3 component (300-580 ms). Colored circles indicate significant SRC (blue) and Flanker conflict (green) amplitude differences. Black crosses show electrodes with significant SRC induced latency effect.

There was also a significant interaction of *Laterality* x *SRC* x *Age*, however, post-hoc analysis did not reveal any significant differences. The factors *Frontality* ($F(2,39)= 13.62$; $p < .001$), *Laterality* ($F(2,39)= 4.65$; $p = .012$) and *Age* ($F(1,40)= 7.11$; $p = .011$) was significant for N2

latency. The significant age effect resulted from delayed N2 component peaks in elderly (M = 291.61 ms; SEM = 3.56) in comparison to young participants (M = 277.49 ms; SEM = 3.92). N2 latency was increased over central (M = 276.61 ms; SEM = 3.37) compared to frontal (M = 290.83 ms; SEM = 2.82; p < .001) and frontocentral (M = 286.20 ms; SEM = 3.07; p < .001) electrodes. Furthermore, there was a significant interaction of *Frontality* x *Age* (F(2,39)= 6.47; p = .002) We found significant latency differences between central (M = 264.54 ms; SEM = 5.00), fronto-central (M = 279.17 ms; SEM = 4.56) and frontal (M = 288.75 ms; SEM = 4.18) electrodes all in young subjects (all ps < .001). Elderly individuals elicited no differences of N2 latencies between the three *Frontality* conditions (frontal: M = 292.91 ms; SEM = 3.80; frontocentral: M = 293.22 ms; SEM = 4.12; central: M = 288.68 ms; SEM = 4.54; all ps > .050). We furthermore found a significant interaction of *Frontality* x *Flanker* (F(2,39) = 4,82; p = .011). A significant Flanker effect was only detectable over frontal electrodes (Flanker incongruent: M = 288.67 ms; SEM = 3.05; Flanker congruent: M = 293.39 ms; SEM = 2.98; p = .044). No significant main effects were found for the factors *Flanker* (F(1,40) = 0.37; p < .546) and *SRC* (F(1,40) = 0.01; p < .914).

3.3.2.3. P3

The analysis of the peak amplitude in the P3 time window yielded significant differences for the factors *SRC* (F(1,40) = 24.55; p < .001) and *Flanker* (F(1,40) = 21.80; p < .001). In both cases amplitudes were decreased in incongruent conflict trials (SRC: M = 4.73 µV; SEM = 0.35; Flanker: M = 479 µV; SEM = 0.35) in contrast to congruent trials (SRC: M = 5.29 µV; SEM = 0.36; Flanker: M = 5.23 µV; SEM = 0.37). There also was a significant interaction of *Laterality* x *Frontality* x *Flanker* x *SRC* x *Age* (F(4,37) = 2.56; p = .041). This interaction is based on the fact that in elderly participants almost every comparison of the respective conflict conditions (fcsc-fcsi; fcsc-fisc; fisc-fisi; fcsi-fisi) was significant over every electrode included in the analysis (all ps < .045), except of the comparison of the single Flanker incongruent (M = 4.95 µV; SEM = 0.56) and the double congruence condition (M = 5.42 µV; SEM = 0.56) (fcsc-fisc) over the Pz electrode (p = .055). In contrast, significant differences in young adults were only found for the single Flanker incongruent compared to the double congruent condition (fcsc-fisc) over Pz (single Flanker incongruent: M = 5.98 µV; SEM = 0.62; double congruent: M = 6.57 µV; SEM = 0.61; p = .009) and the single SRC condition compared to the double congruent condition (fcsc-fcsi) over the electrodes P1 (single SRC incongruent: M = 5.74 µV;

SEM = 0.59; double congruent: M = 6.36 µV; SEM = 0.62; p = .027), Pz (single SRC incongruent: M = 5.91 µV; SEM = 0.59; double congruent: M = 6.57 µV; SEM = 0.61; p = .016) and P2 (single SRC incongruent: M = 5.29 µV; SEM = 0.53; Flanker congruent: M = 5.94 µV; SEM = 0.56; p = .026).

Significant main effects of P3 latency were found for the factors *Frontality* ($F(2,39) = 4.48$, $p = .014$), *Laterality* ($F(2,39) = 10.09$, $p < 0.001$) and *Age* ($F(1,40) = 30.48$, $p < 0.001$). The latency over parietal electrodes (M = 440.77 ms; SEM = 8.56) was shorter than over centroparietal (M = 460.78 ms; SEM = 7.69) recording sites (p = .002). In addition, P3 latency was shorter over right electrodes (M = 459.41 ms; SEM = 6.67) than over the scalp midline (M = 459.70 ms; SEM = 6.58; p < .001) and the left side (M = 444.174 ms; SEM = 7.66; p = .004). Elderly participants (M = 490.88 ms; SEM = 8.89) showed an increased P3 latency in comparison to young adults (M = 418.00 ms; SEM = 9,77). Furthermore, there was a significant interaction of *Frontality* x *Age* ($F(2,39) = 10.09$; $p < .001$), of *SRC* x *Age* ($F(2,39)= 4.25$; $p = .046$) and *Frontality* x *SRC* x *Flanker* x *Age* ($F(2,39)= 3.71$; $p = 0.028$). Further analysis of the interaction of the four factors revealed that in young participants the peak latency in the single Flanker incongruent (fisc; M = 423.11ms; SEM = 13.94) respectively the single SRC incongruent (fcsi; M = 430.79 ms; SEM = 14.39) condition was significantly delayed when compared to the double congruence condition (fcsc; M = 401.39 ms; SEM = 10.43) over centroparietal electrodes (fisc-fcsc: p = .011; fcsi-fcsc: p = .012). These comparisons were not significant in elderly participants (fcsc: M = 503.40 ms; SEM = 9.48; fisc; M = 504.13ms; SEM = 12.67; fcsi; M = 486.44 ms; SEM = 13.07; fisc-fcsc: p = .952; fcsi-fcsc: p = .267).

In summary, the P2 amplitude was modulated by the Flanker conflict in both groups, while in the SRC task condition a conflict induced increase of the P2 amplitude was only found in elderly subjects. Furthermore, the N2 amplitude was increased in response to incongruent Flanker trials in both groups but more pronounced in young adults. The N2 latency was delayed in the congruent Flanker condition over frontal electrodes. There were also age-specific differences with respect to the P3 amplitude. While young adults only showed Flanker and SRC conflict effects on the P3 amplitude over parietal electrode positions, elderly subjects exhibited a more pronounced and widespread modulation of the P3 amplitude over central, contro-parietal, and parietal recording sites. The latency of the P2, N2, and P3 component was

delayed in elderly compared to young participants. A conflict induced P3 latency increase for both conflict types was only found in young adults over centro-parietal regions.

3.4. Discussion

In the present study a combined Flanker and SRC conflict task was employed to investigate how ageing affects different processing stages of conflict resolution and whether these effects are specific for different conflict types. The present data substantiate the findings of previous studies (Kawai et al., 2012; Sebastian et al., 2013) and additionally demonstrate that the effects of ageing seem to be distinctive for different conflict types in early stages of information processing as indicted by the P2 and N2 component. Specifically, the group of elderly participants showed an increased amplitude modulation of the P2 component in the SRC task condition, whereas, the N2 amplitude modulation in response to the Flanker conflict condition was relatively decreased in comparison to young controls. Conflict induced amplitude modulation in later stages of processing indicated by the P3 component was enhanced in elderly individuals for both conflict types.

Behavioral data

The comparison of behavioral effects yielded a significant effect of both conflict types with increased RTs in response to the SRC and the Flanker conflict and higher error rates in response to the SRC. The ANOVA of the behavioral performance did not reveal any conflict effect differences between both groups, however, when the respective effects were analyzed across different RT quartiles, an age-related increase of the SRC effect was evident in rather slow responses (third quartile). Variations of the SRC effect in dependence of response speed were detected in several studies (De Jong et al., 1994; Frühholz et al., 2011; Juncos-Rabadán et al., 2008). Importantly, RT quintile analyses across different age-groups revealed that the interrelation of RT and SRC effect differs between elderly and young adults. (Juncos-Rabadán et al., 2008; Castel et al., 2007). In the present data, the SRC effect increases with slower responses in both groups. However, this effect is more pronounced in elderly, leading to significant SRC effect differences in slower responses. This age-specific interrelation of response speed and SRC effect probably also explains why the SRC effect consistently differed in every quartile between both groups in the fMRI session. EEG and fMRI are associated with specific recording characteristics. It is well documented that participants show slower responses

during fMRI in comparison to EEG recording (van Maanen et al., 2015). This holds also true for the present data. Thus, due to the differences of response speed in both sessions, age-specific differences of the SRC effect manifest more strongly during fMRI recording. Importantly, the Flanker conflict effect did not differ between both groups in all quartiles of both sessions.

These results are in line with previous studies that demonstrated that ageing is associated with increased SRC effects of behavioral measures in elderly, while the Flanker conflict effect is not increased in advanced age (Kubo-Kawai and Kawai, 2010; van der Lubbe and Verleger, 2002). This is also illustrated by studies investigating both tasks in the same experimental setting (Kawai et al., 2012). Together, these data suggest that the processing of the SRC is particularly susceptible to ageing effects, whereas the resolution of the Flanker conflict remains relatively unaffected by increasing age.

Electrophysiological data

The P2 amplitude was increased in Flanker incongruent trials in comparison to Flanker congruent trials in both groups, while only elderly elicited an amplitude enhancement in response to the incongruent SRC task condition. The sensitivity of the P2 amplitude to conflict processing was also reported by Gajewski et al. (2008) who found that the P2 amplitude is increased in incompatible compared to compatible trials in a response-cueing task in healthy young adults. Similar results were reported by West and colleagues (2004) using a numerical conflict task. However, the present study additionally showed that the conflict induced modulation of the P2 significantly differs between the two conflict types and age groups. One explanation for the altered SRC processing in advanced age is that elderly experience more difficulties while processing distractors that are confounded with the target stimulus (Proctor et al., 2005). Several studies found that the P2 amplitude is associated with stimulus evaluation processes (Gajewski et al., 2008; Potts, 2004). In these studies the P2 amplitude was enhanced when a specific target characteristic became task relevant. Another study which introduced an oddball task (Kim et al., 2008) reported the P2 amplitude to be increased when the detectability of the relevant and irrelevant stimulus feature is decreased. Thus, the modulation of the P2 amplitude possibly reflects higher efforts associated with successful stimulus classification. Similar results were obtained by Riis and colleagues (2010). They demonstrated that the P2 amplitude is elevated in response to novel stimuli and thus argued that the P2 is reflects cognitive processes related to the mismatch of deviant stimuli with a standard stimulus set. Importantly, this effect is particularly pronounced in elderly, indicating that the matching

process is possibly enhanced in order to compensate for age-related alterations regarding other cognitive mechanisms. The augmented modulation of the P2 amplitude in elderly in the present study possibly indicates similar mechanisms. Several studies demonstrated that particularly the difficulty to suppress the processing of distractor stimuli contributes to the decline of conflict processing in elderly, while the processing of relevant stimuli is relatively spared from detrimental ageing effects. The correct identification of the irrelevant stimulus is particularly difficult in the SRC task, because relevant and irrelevant features are confounded in the same stimulus. Thus, elderly possibly enhance evaluation mechanisms by engaging more cognitive resources to promote the correct discrimination of relevant and irrelevant information input.

In various ERP studies on conflict tasks incongruent trials exhibited higher N2 amplitudes than congruent trials (for review see Folstein and Van Petten, 2008). The N2 was thus associated with early inhibitory execution and monitoring processes. Further evidence for this hypothesis is also provided by studies using a source analysis approach (Bekker et al., 2005; Wascher et al., 2011) that located the neural generators of the N2 in the medial PFC, a brain area associated with conflict monitoring, conflict detection, and response selection (Carter et al., 1998; Kiehl et al., 2000; Liu et al., 2004; van Veen and Carter, 2002). In the present study, we also found an increase of the N2 amplitude in response to incongruent Flanker stimuli, however, there was no modulation of the N2 component by the SRC task in both groups. Similar results were obtained in a previous study (Frühholz et al., 2011). Thus, the monitoring and response selection mechanisms indexed by the N2 component seem to be specifically related to the Flanker conflict. These data corroborate reports that argue for independent neural mechanisms for the resolution of different conflict types (Egner et al., 2007; Nee et al, 2007). The present results additionally show that the N2 amplitude in younger adults is generally more pronounced and also shows a slightly stronger Flanker conflict induced amplitude modulation compared to older adults. An age-related attenuation of the N2 amplitude and a reduced susceptibility to Flanker conflict interference has already been reported in previous studies (Amenedo and Diaz, 1998; Pekkonnen et al., 1996; Wild-Wall, 2008). Wild-Wall and colleagues (2008) argued that the more pronounced N2 component in younger subjects possibly reflects a stronger interference induced by the Flanker stimuli. They concluded that elderly reduce interference by narrowing the focus of attention to the central target stimulus. This is in line with the assumption that elderly are able to inhibit distractors that are not confounded with the target stimulus more efficiently. The effects of ageing on the N2 amplitude and the associated cognitive mechanisms during Flanker task processing seem to have less profound consequences for the conflict resolution process. Flanker conflict effects were found to be stable across

different age groups (Kawai et al., 2012). Furthermore, in contrast to SRC resolution young and elderly subjects elicit similar activation patterns during Flanker conflict resolution, suggesting similar processing mechanisms in both groups. Analysis of N2 latency revealed that in elderly individuals the component peak is delayed in comparison to young adults. This result accords with previous results of ageing effects on the N2 component.

In addition, N2 scalp distributions differed in young and elderly subjects. Young adults elicited peak amplitudes in the N2 time frame over frontal electrode positions while in elderly participants the N2 was most pronounced over central electrodes.

In accordance with previous studies (Van der Lubbe and Verleger, 2002; Wild-Wall et al., 2008) the present data analysis revealed age-related differences of the conflict-induced P3 amplitude modulation. Both, the SRC and the Flanker conflict task conditions were associated with a significantly reduced P3 amplitude extending over parietal and central recording sites in elderly subjects. In contrast, young adults demonstrated distinct conflict induced amplitude changes. Since the P3 amplitude has been shown to reflect the amount of attentional resources (Polich and Heine, 1996), the decreased P3 amplitude in incongruent trials might indicate that elderly individuals consume more cognitive resources due to higher task demands. Furthermore, the P3 amplitude was also associated with motor inhibition processes (Smith et al. 2007). The decrease of P3 amplitude in the various conflict conditions thus might also be attributed to an increased need for inhibition of incorrect response activity in elderly subjects. Importantly, the age-related changes of P3 amplitude responsiveness were found similarly in both conflict types. Falkenstein et al. (2002) found that ageing effects on the P3 component are less specific regarding task context than the effects on the N2 component. This finding might indicate that in contrast to the earlier task associated information processes ageing seems to affect motor inhibition in Flanker and SRC task conditions in an equal manner.

Taken together, ageing effects on conflict processing seem to be specific for conflict type and the time window of information processing. While age-related differences were distinctive for both the Flanker conflict and the SRC in early time windows (P2 and N2 component), in later stages of information processing associated with motor inhibition (P3 component) Flanker and SRC interference were equally affected in the elderly participant group. These data, in addition to the findings of Experiment 1, suggest that the specificity of ageing effects on interference control is particularly associated with early information processing stages such as stimulus evaluation and conflict detection.

4. Experiment 3

4.1. Introduction

A substantial part of aMCI research focuses on memory dysfunction. Nevertheless, there is increasing evidence, that this subtype is also associated with alterations of executive functions such as working memory, cognitive flexibility and also interference control (Brandt et al., 2009; Traykov et al., 2007; Chang et al., 2010; Johns et al., 2012). Deficits of executive functions in individuals with aMCI impede activities of daily living and promote the conversion to AD (Marshall et al., 2011; Chapman et al., 2011) and are furthermore linked to increased cortical thinning (Chang et al., 2010). Moreover, the occurrence of executive dysfunctions is associated with particularly low memory scores in patients with aMCI (Chang et al., 2010). Deficiencies of interference control are known to cause memory deficits associated with healthy ageing (Hasher and Zacks, 1988) and thus might also cause or at least aggravate memory deficits in aMCI. Indeed, there is evidence that the reduction of distracting information improves memory performance in aMCI patients (Della Sala., 2005). These studies highlight the critical role of interference control in the transition from healthy to pathological ageing. However, studies focusing on interference processing in individuals with aMCI and early AD are sparse and inconsistent. Zhang et al. (2007) found no decline of inhibitory function with standard neuropsychological tests such as the Stroop task in patients with aMCI. Another study employing the Simon task did not find any behavioral differences between adults with and without aMCI as well (Cespón et al., 2014). In contrast, Traykov et al. (2007), Li et al. (2009) and Belanger et al. (2010) detected that elderly with aMCI performed worse in the Stroop task than healthy controls. Further evidence is provided by Wylie et al. (2007) who found that participants with aMCI exhibit an increased Flanker conflict effect when compared to healthy elderly. These conflicting results possibly go back to the diversity of inhibitory functions: different conflict tasks tap different subcomponents of inhibition that rely on different neural mechanisms. Furthermore, these components undergo distinctive alterations with increasing age as delineated in different studies (Sebastian et al., 2013; Turner and Spreng, 2012; Kawai et al., 2012) and also in Experiment 1 and 2 of the present thesis. Thus, the pathological alterations associated with aMCI might also affect different conflict types in different ways. In addition, alterations of cognitive processing that accompany aMCI might be too subtle to consistently cause significant deviations of behavioral performance. Methods such as fMRI and EEG offer the possibility to investigate the neural mechanisms underlying

interference control and thus detect alterations of conflict processing that do not manifest in changes of reaction times and error rates.

Li et al. (2009) demonstrated that compared to healthy elderly, individuals with aMCI exhibit increased activation of prefrontal and parietal areas in response to the Stroop conflict. Kaufmann and colleagues (2008) also observed additional recruitment in the aMCI group during Stroop conflict processing, however, in this study increased activation was mainly located in posterior brain areas including the temporal and the occipital cortex. Several studies showed that increased (prefrontal) activation serves as a compensation strategy in healthy elderly (Cabeza et al., 1997; Grady et al., 1998; Reuter-Lorenz et al., 2000). Thus, patients with aMCI possibly also engage compensatory mechanisms during conflict resolution. However, there is also evidence that neural overrecruitment in elderly with aMCI does not reflect beneficial compensation mechanisms but rather represents cognitive and neural dysfunction (Bakker et al., 2012). Moreover, it is striking that in the study by Kaufmann and colleagues (2008) participants with aMCI additionally recruited areas that are not specifically related to conflict processing (Nee et al., 2007). Bokde and colleagues (2008) additionally found more diffuse activation patterns in patients with aMCI in a face and location matching task. These findings correspond to the dedifferentiation theory proposed by Baltes and Lindenberger (1997). According to this theory, ageing is accompanied by a decrease of neural specificity and thus less specific (more diffuse) activation patterns. Hence, the results illustrated by Kaufmann et al. (2008) and Bokde et al. (2008) possibly reflect a decrease of neural specificity in individuals with aMCI. Nevertheless, due to the limit number of studies it is difficult to delineate whether aMCI is associated with specific alteration of neural processing – particularly in the context of interference control.

The investigation of ERPs such as the P2, N2 and the P3 that are typically associated with interference control in patients with aMCI are very sparse as well. In healthy elderly the N2, the amplitude is diminished in comparison to young adults and the amplitude modulation induced by conflict tasks seems to be reduced as well. Furthermore, the peak latency of the N2 is delayed with increasing age. There are hints that these effects on the N2 component are even more pronounced in elderly with aMCI. Alterations of the N2 component in patients with aMCI are also found in the context of conflict processing, however, these results are inconsistent: Wang et al. (2013) found that the N2 component is less pronounced in patients with aMCI and AD compared to healthy controls in Flanker task. However, there was no interaction of group and condition suggesting that Flanker induced modulation of the N2 amplitude did not differ

between the groups. Cespón et al (2014) found that the N2 latency was increased in patients with aMCI that were also impaired in other domains than memory indicated by standard neuropsychological tests (multiple domain aMCI) in a Simon task while the N2 amplitude did not differ between both groups. Studies investigating the P3 component in aMCI also obtained inconsistent results. There are studies that detected latency differences of the P3 component between adults with and without aMCI (Golob et al., 2001, Li et al., 2010) but there are also studies without any significant group differences regarding the P3 (Cespón et al., 2014). The P2 component reflects early cognitive mechanisms of conflict processing associated with stimulus evaluation (Potts, 2004). Ageing effects on the P2 component have been detected across different tasks (McEvoy et al., 2001, Riis et al., 2009). West and Alain (2000) observed that the P2 amplitude is also increased in elderly during conflict processing. Furthermore, Experiment 2 of the present thesis revealed that healthy elderly exhibit an increased SRC amplitude effect when compared to young controls. Whether the onset of cognitive impairments as found in patients with aMCI has an effect on the cognitive mechanisms underlying the P2 is unclear. There are studies that verified changes of electrophysiological correlates in very early stages of information processing between participants with and without aMCI. However, these studies refer to the MMN and only report amplitude differences over occipital recording sites. Thus, it is unclear whether these effects are also detectable over frontal electrodes where the anterior P2 component is located.

The combined SRC and Flanker conflict task employed in the present study provides the possibility to examine whether and how different components of interference control are impaired. Participants underwent EEG and fMRI recording to evaluate whether aMCI is associated with altered temporo-spatial dynamics of neural processing of interference control.

4.2. Methods

4.2.1. Participants

Participants with aMCI were recruited from Bremen Ost Clinic and were pre-diagnosed by an experienced neuropsychologist. The participants underwent another neuropsychological evaluation at the Bremen University with the neuropsychological tests described in chapter 1.4.1. Diagnostic criteria for aMCI corresponded to Peterson (2004).

Table 4 Results of the neuropsychological evaluation. "Divided attention" and "Alertness" are parts of the Testbatterie zur Aufmerksamkeitsprüfung (TAP). The indicated p-values were obtained with a two-sample t-test. (NAI = Nürnberger Alters Inventar, IADL = instrumental activities of daily living, MMSE = Mini Mental State Examination, VLMT = Verbaler Lern und Merkfähikeitstest, TMT = Trail Making Test, RWT = Regensburger Wortflüssigkeitstest, SD = standard devation)

	Healthy Elderly		aMCI		
	mean	SD	mean	SD	*p*-value
Age	71.3	2,15	69.1	3,99	.126
NAI (activities of daily living)	25.5	3,30	26.7	3,27	.150
IADL	7.8	0,40	7.3	1,12	.245
GDS	2.0	2,24	3.0	3,46	.431
MMSE	28.7	1,10	27.6	1,75	.095
MWT-B	33.1	2,02	32.8	2,96	.803
Rey Figure Test					
copy	34.6	1,43	35.2	0,98	.310
short delay	20.1	5,94	21.4	6,04	.610
long delay	19.7	5,05	18.6	8,19	.699
VLMT					
trial 1 to 5	43.7	7,89	35.2	6,51	.012
trial 6	8.4	2,16	3.8	2,56	< .001
trial 7	8.2	2,36	3.1	1,81	< .001
trial 5-6	2.6	1,96	4.9	1,64	.008
trial 5-7	2.8	1,89	5.4	1,50	.002
recognition	13.6	1,63	11.3	3,80	.072
recognition (corrected)	10.2	4,87	5.4	4,73	.015
TMT					
A	44.0 s	12,66	39.6 s	7,28	.334
B	98.4 s	38,59	89.5 s	22,30	.515
Digit Span					
forward	6.5	1,44	8.0	1,67	.041
backward	5.1	0,94	5.8	1,66	.222
Block Span					
forward	7.2	2,18	7.3	1,56	.912
backward	6.4	2,20	6.5	1,63	.828
Alertness					
with warning signal	285.8 ms	43,08	280.1 ms	52,01	.781
without warning signal	287.0 ms	44,24	270.4 ms	24,16	.287
Divided Attention					
visual stumulus	850.0 ms	98,97	836.6 ms	63,61	.710
auditiory stimulus	580.8 ms	80,56	605.9 ms	92,90	.506
errors	1.4	0,92	1.7	1,56	.513
omissions	1.5	1,37	3.0	2,97	.132
RWT					
words with "S"	18.6	7,15	17.5	6,79	.717
"animals"	34.4	7,24	26.8	7,45	.026

The VLMT was used to evaluate memory performance. Participants with aMCI were included when they performed 1.5 SD below the age-adjusted mean in the delayed recall trial (seventh trial) of the VLMT. The subdivision of single and multiple domain aMCI was not relevant for the recruitment. Since the aMCI group included only 11 male participants, female adults from the healthy control group were excluded for further analysis. Due to low data quality, one male elderly of each group had to be excluded from fMRI analysis. Thus, 11 male elderly with (mean age 69.09 years, SD = 3.99) and without aMCI (mean age 71.27 years, SD = 2.15) were included in the ERP analysis and 10 male elderly with (mean age 69.50 years, SD = 3.95) and without aMCI (mean age 71.40 years, SD = 2.22) were included in the fMRI analysis. All participants were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1970) and had normal or corrected to normal vision. There were no reports of significant psychiatric and neurological disorders.

4.2.2. Stimulus material

The task design is described in chapter 1.4.1. The four experimental conditions (congruent Flanker and SRC condition (FcSc); incongruent Flanker and congruent SRC condition (FiSc); congruent Flanker and incongruent SRC condition (FcSi), and incongruent Flanker and SRC condition (FiSi)) were presented in six blocks of 60 trials separated by short breaks of 10 seconds. There were 72 trials of each condition. Trial sequence was pseudo-randomized to avoid effects of trial succession. Each trial started with a white fixation cross on black background in the center of the screen (800 ± 150 ms). Thereafter, the set of arrows appeared for 250 ms followed by a blank screen for 2000 ms. During EEG recording participants were seated in front of the screen with a viewing distance of 60 cm. The experiment was conducted in a darkened room. Stimuli were presented on a computer screen (refresh rate 60 Hz) using Presentation Software (neurobehavioral Systems; https://nbs.neuro-bs.com). A JVC video projector was used to display the stimuli onto a projection screen at the rear end of the fMRI scanner with a viewing distance of about 38 cm.

4.2.2. Image acquisition

A 3-T SIEMENS Magnetom Allegra System (Siemens, Erlangen, Germany) with a T2*-weighted gradient echo-planar imaging (EPI) sequence (28 contiguous slices aligned to AC-PC place, slice thickness 4mm, no gap, TR = 1.5 s, TE = 30 ms, FA = 73°, in-plane resolution 3 mm x 3 mm) and a manufacturer supplied circularly polarized head coil signal was used for functional imaging data acquisition.

4.2.3. Image analysis

Statistical Parametric Mapping software SPM (Version 5; Welcome Department of Cognitive Neurology, London, UK) was used for the preprocessing and the analysis of the functional data. The first ten volumes of each functional data set were discarded. Preprocessing included re-alignment to the first volume, slice-time correction, spatial normalization to the standard SPM EPI template in MNI space and smoothing with a 8 mm x 8 mm x 10 mm full width at half maximum (FWHM) Gaussian kernel. Data were high-pass filtered (128Hz) to remove low frequency signal drifts. A first-order autoregression model (AR-1) was used to correct temporal autocorrelations.

Regressors were defined by delta functions convolved with a canonical HRF at each stimulus onset. The design matrix comprised regressors “FcSc”, “FiSc”, “FcSi”, “FiSi”, “neutral” (only trials with correct responses were included), an additional regressor “errors” for all trials with incorrect responses, as well as six motion regressors. The parameters for the motion regressors were obtained during realignment.

Contrasts for each conflict condition against to the double incongruent condition ([Fisc > FcSc]; [FcSi > FcSc]; [Fisi > FcSc]) was calculated for every participant. The different contrasts were separately analyzed with a one sample t-test for both groups to obtain neural activation specific for group and conflict type. Group differences for each contrast were investigated with a two sample t-tests with healthy elderly and elderly with aMCI as independent groups. Contrasts were thresholded at $p < .001$ (uncorrected) combined with a cluster extent threshold of k=15. Group contrasts were thresholded at $p < .005$ ($k = 15$). Additionally, the respective contrasts of each group were used as an inclusive mask (thresholded at $p < .005$; uncorrected) to exclude task irrelevant activation differences. We used

the conjunction null hypothesis (Nichols et al., 2005; $p < .005$ (uncorrected), $k = 15$.) for each contrast to identify common activation patterns

4.2.4. EEG recording and offline processing

EEG recording was conducted with 64 channels. Ag-AgCl electrodes were attached to an elastic cap according to the 10-10-system and referenced to an electrode on the nose tip (Nz) with an impedance of less than 5 kΩ. EEG signal was amplified by a REFA® multi-channel system (TMS International; www.tmsi.com) and digitized with a sampling rate of 512 Hz. Eye movements and blinks were monitored with vertical and horizontal electroencephalogramm (EOG).

Offline processing included bandpass filtering at 0.1-20 Hz and referencing to average reverence. Stimulus-locked time epochs of 900 ms (100 ms pre- and 800 ms post-stimulus) were averaged for each condition. Epochs with no or incorrect response were discarded from analysis. Each epoch was baseline corrected to the pre-stimulus interval. EOG artifacts were corrected using an algorithm introduced by Ille et al. (2002). Epochs were visually inspected for artifacts. Only epochs without artifacts caused by eye movements or blinks were used for further analysis.

4.2.5. ERP analysis

The different ERPs were determined via visual inspection of the grand average waveforms of all conditions for both groups. For each component a time window that corresponded to the respective component peaks was defined for further analysis. Afterwards the mean amplitude was calculated for every time window for every participant. ERP research indicates that the different ERP components are characterized by different topographies. Thus, in accordance with previous reports and the topographies in the present data, different electrodes were included for the analysis of the different components.

The P2 became evident over frontal electrodes around 190 ms after stimulus onsets in both groups. For the amplitude analysis of the P2, consequently a time frame of 170 – 210 ms was chosen. The frontal topography of the P2 was also observed in other studies (Riis et al., 2009; Potts, 2004), thus the electrodes Fz, FCz and Cz were included in the P2 analysis. The N2

appeared at about 290 – 300 ms over central electrodes with a slight extension to centroparietal electrodes. The N2 is frequently detected over frontal electrodes in young elderly, however, with increasing age the N2 topography shows a more posterior orientation. Accordingly, the N2 amplitudes were analyzed for the time window of 260 – 340 ms over the electrodes FCz, Cz and CPz. Furthermore, there was a positive deflection over parietal electrodes that corresponds to the P3b component. In contrast to the P2 and N2, the P3 component was temporally more extended: the deflection started around 400 ms, increased until 460 ms and started to decrease at about 570 ms. In accordance, the P3 time frame ranged from 460 – 570 ms. The electrodes CPz, Pz and POz were included in the P3 analysis.

Mean amplitudes were entered into an 2 x 2 x 2 x 3 ANOVA with the within subject factors SRC (congruent vs. incongruent), Flanker (congruent vs. Incongruent) and Electrode (Fz vs. FCz vs. Cz for P2 analysis; FCz vs. Cz vs. CPz for N2 analysis; CPz vs. Pz vs. POz for P3 analysis) and the between subject factor Group (aMCI vs. healthy controls). Greenhouse-Geisser epsilon correction was applied when assumption of sphericity was violated. LSD post-hoc t-tests with a significance level of $\alpha = 0.05$ were conducted to compare the levels of the respective main factors. Post-hoc Student's t-tests were used to examine significant factor interaction ($\alpha = 0.05$).

4.3. Results

4.3.1. Neuropsychological evaluation

A t-test for independent groups was conducted to compare the performance scores of elderly with aMCI and healthy controls obtained in the neuropsychological evaluation. The results are illustrated in *Table 4*. The results confirm differences of episodic verbal memory performance between both groups. The deficits are found in the encoding phase (trial 1 to 5), in the short and long delayed free recall (trial 6 and 7) and also in the recognition trial. The results further suggest a decrease of verbal fluency in the semantic category in elderly with aMCI. These results indicate that the recall of semantic information is relatively impaired in participants with aMCI. Group differences of attention, executive functions, non-verbal memory and visuo-spatial functions are not indicated.

4.3.2. Behavioral data

Reaction times and error rates were entered to a 2 x 2 x 2 ANOVA with the factors *Flanker*, *SRC* and *Group*. Analyses were performed separately for the EEG and the fMRI session. RTs and error rates for the different conditions, recording sessions and groups are depicted in *Figure 10* and *11*. In both sessions reaction times were increased in incongruent (EEG: M = 620 ms; SEM = 23.72; fMRI: M = 687 ms; SEM = 24.98) compared to congruent (EEG: M = 585 ms; SEM = 21.47; fMRI: M = 650 ms; SEM = 23.37) Flanker trials (EEG: $F(1,20)= 46.59$; $p < .001$; fMRI: $F(1,18)= 31.84$; $p < .001$).

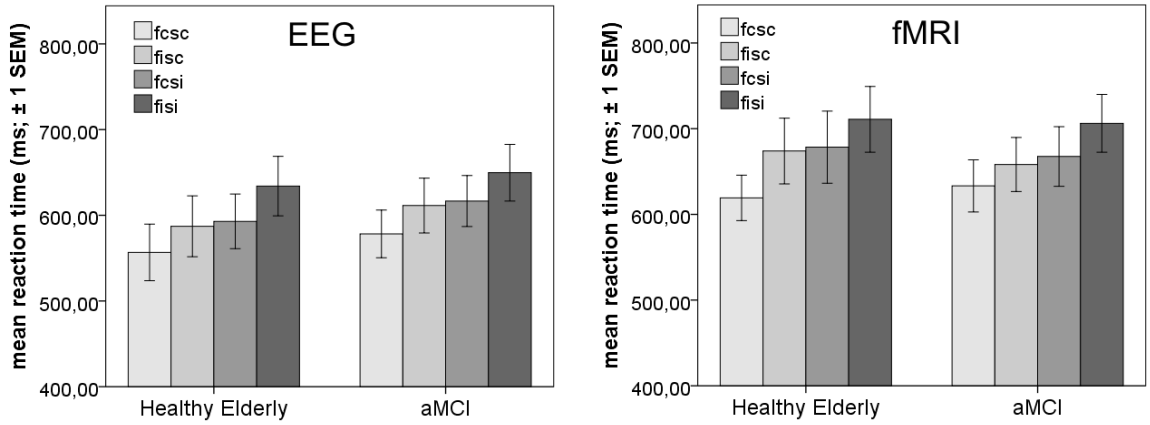

Figure 10 Reaction times for the EEG and the fMRI session. Error bars show the standard error of the mean (SEM)

There was also a main effect for the factor *SRC* in both sessions (EEG: $F(1,20) = 46.80$; $p < .001$; fMRI: $F(1,18) = 35.31$; $p < .001$). Reactions were faster in congruent (EEG: M = 583 ms; SEM = 22.58; fMRI: M = 618 ms; SEM = 22.70) than in incongruent (EEG: M = 623 ms; SEM = 22.77; fMRI: M = 659 ms; SEM = 24.94) SRC trials. There was no difference of RTs between the groups (EEG: $F(1,20) = 0.22$; $p = .641$; fMRI: $F(1,18) = 0.05$; $p = .835$). The SRC additionally elicited increased error rates in the incongruent (EEG: M = 6.16 %; SEM = 1.47; fMRI: M = 6.56 %; SEM = 2.19) compared to congruent (EEG: M = 1.64 %; SEM = 0.30; fMRI: M = 2.05 %; SEM = 0.53) condition in both recording sessions (EEG: $F(1,20) = 11.26$; $p = .003$; fMRI: $F(1,18) = 6.01$; $p = .025$). The difference between Flanker congruent and incongruent trials was not significance in both sessions (EEG: $F(1,20) = 3.59$; $p = .073$; fMRI: $F(1,18) = 2.25$; $p = .151$). Error rates did not differ between the groups (EEG: $F(1,20) = 0.22$; $p = .641$; fMRI: $F(1,18) < 0.01$; $p = .985$).

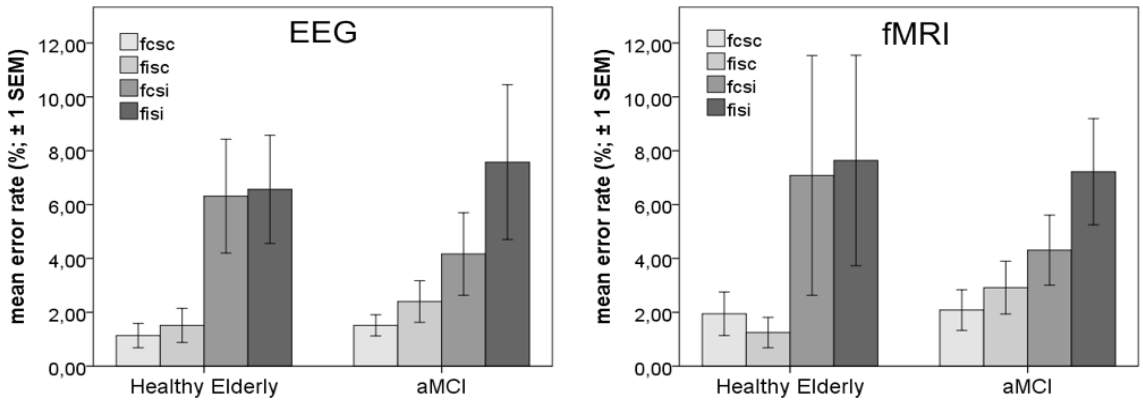

Figure 11 Error rates for the EEG and fMRI session. Error bars show the standard error of the mean (SEM).

Taken together, RTs were consistently modulated by both conflicts in both sessions. The SRC yielded higher error rates in incongruent trials, while the Flanker conflict did not affect error rates.

4.3.3. ERP results

P2

The analysis of the P2 amplitude yielded a significant main effect of the factor *Electrode* ($F(2,19) = 31.10$, $p < .001$). The amplitude was higher over Fz (M = 4.58 µV; SEM = 0.46) than over Fz (M = 5.02 µV; SEM = 0.44; $p < .001$) and Cz (M = 2.85 µV; SEM = 0.30; $p < .001$). The amplitude difference between FCz (M = 4.48 µV; SEM = 0.36) and Cz was additionally significant ($p < .001$). Furthermore, there was a significant effect of the factor *Flanker* ($F(1,20) = 6.38$, $p = .020$) due to increased amplitudes in Flanker incongruent (M = 4.26 µV; SEM = 0.33) compared to Flanker congruent (M = 3.98 µV; SEM = 0.34) trials. The factors *SRC* ($F(1,20) = 2.47$, $p = .131$) and *Group* ($F(1,20) = 0.10$, $p = .753$) were not significant. However, there was an interaction of *SRC x Group* ($F(1,20) = 5.53$, $p = .029$) showing that the difference between SRC congruent (M = 3.85 µV; SEM = 0.47) and incongruent (M = 4.19 µV; SEM = 0.48) trials was only present in healthy elderly ($p = .002$), while this comparison was not significant in participants with aMCI (congruent: M = 4.26 µV; SEM = 0.47; incongruent: M = 4.20 µV; SEM = 0.47; $p = .556$; see *Figure 14*).

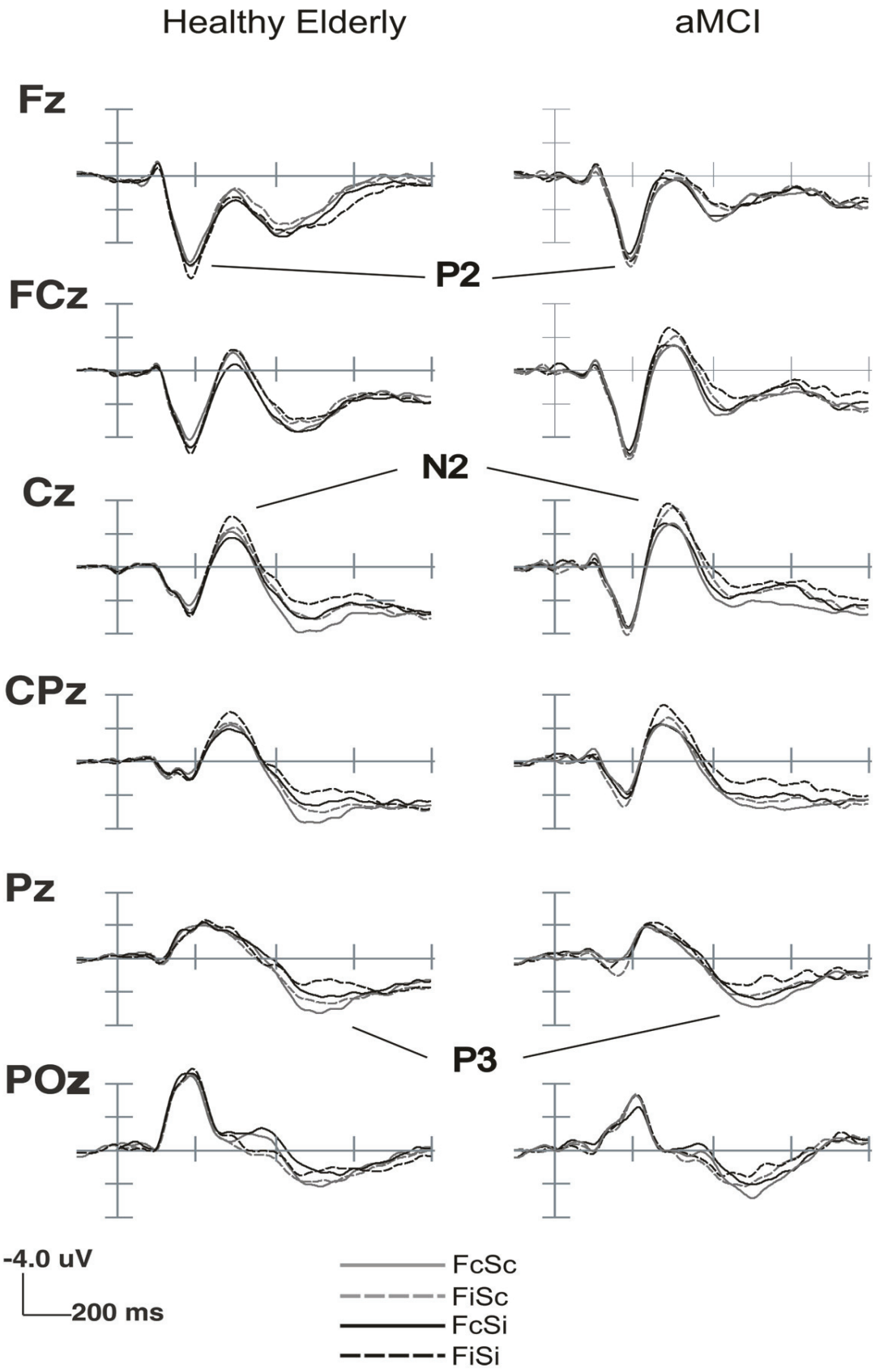

Figure 12 Group-averaged event-related potentials for the conditions FcSc (Flanker and SRC congruent), FiSc (Flanker incongruent, SRC congruent), FcSi (Flanker congruent, SRC incongruent) and FiSi (Flanker and SRC incongruent) for young and elderly adults. Stimulus onset is shown by the vertical line. Ticks on the time axis represent 200 ms.

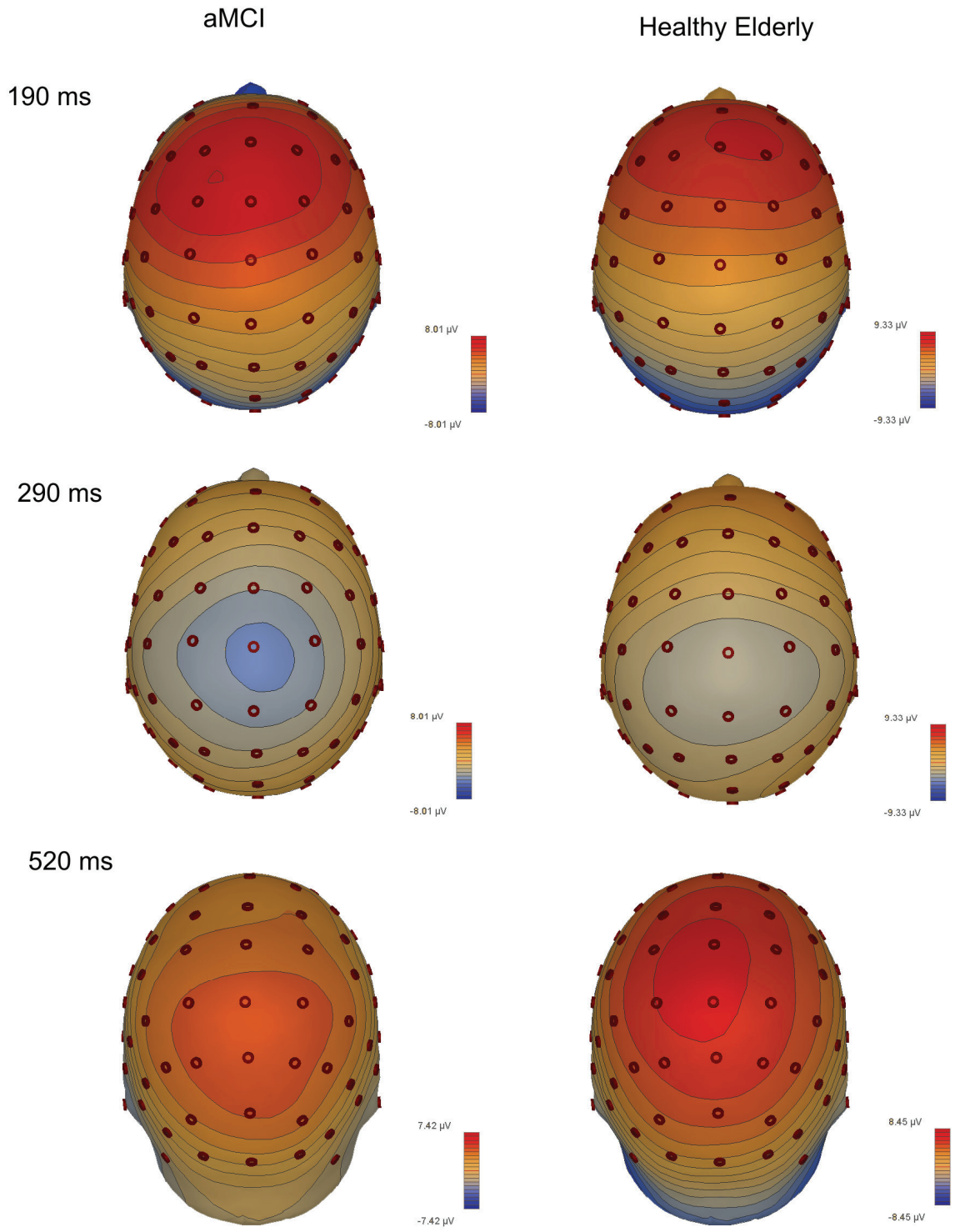

Figure 13 Topography of the P2, N2 and P3 component.

N2

There was a significant main effect of the factor *Electrode* ($F(2,19) = 6.90$, $p = .003$) due to an enhanced amplitude over Cz (M = -2.40 µV; SEM = 0.60) respectively CPz (M = -2.21 µV; SEM = 0.51) compared to FCz (M = -1.04 µV; SEM = 0.59; $p < .001$; $p = .037$). Furthermore, N2 amplitudes were more negative in the incongruent (M = -2.22 µV; SEM = 0.54) than the congruent (M = -1.56 µV; SEM = 0.52) Flanker condition ($F(1,20) = 14.78$, $p < .001$) while no amplitude differences were detected for the factor *SRC* ($F(1,20) = 14.78$, $p < .001$). However, the interaction of *Flanker* x *SRC* revealed that the N2 amplitude in the incongruent Flanker condition (M = -2.40 µV; SEM = 0.55) was only enhanced in comparison to the congruent Flanker condition (M = -1.46 µV; SEM = 0.53) when SRC information was concomitantly incongruent ($p < .001$). In contrast, the N2 amplitude was not enhanced in response to incongruent Flanker stimuli (M = -2.02 µV; SEM = 0.53) in comparison to congruent Flanker trials (M = -1.67 µV; SEM = 0.51) when color and arrow direction were congruent ($p = .102$). Furthermore, the incongruent SRC condition induced more pronounced N2 amplitudes only when Flanker stimuli were also incongruent ($p = .009$). The N2 amplitude was not altered in incongruent SRC trials when Flanker stimuli corresponded with the target ($p = .098$; see *Figure 14*).

P3

P3 amplitude was attenuated in the Flanker incongruent condition trials (M = 1.74 µV; SEM = 0.29) in comparison to the congruent condition (M = 2.17 µV; SEM = 0.33; $F(1,20) = 12.35$, $p = .002$). Incongruent SRC trials (M = 1.58 µV; SEM = 0.51) also reduced the P3 amplitude in comparison to congruent SRC trials (M = 2.34 µV; SEM = 0.51; $F(1,20) = 26.10$, $p < .001$). The interaction of *Flanker* and *Electrode* ($F(2,19) = 5.31$, $p = .019$) indicated that the Flanker effect was only evident over the Pz (Flanker congruent: M = 2.35 µV; SEM = 0.39; Flanker incongruent: M = 1.81 µV; SEM = 0.34) and the CPz electrode (Flanker congruent: M = 2.60 µV; SEM = 0.54; Flanker incongruent: M = 1.98 µV; SEM = 0.51).

Taken together, the analysis of the mean amplitude revealed that Flanker conflict modulated the P2 amplitude in both groups. However, only elderly controls exhibited an increased P2 amplitude in response to the incongruent SRC condition. In contrast, the P2 amplitude was not affected by the SRC in participants with aMCI. The N2 amplitude was enhanced in Flanker incongruent trials, only in conditions with concomitant incongruent SRC information and vice versa. Thus, the N2 amplitude was only enhanced when two sources of interference were

present. Finally, the P3 amplitude was reduced by the incongruent condition of both conflict types in both groups.

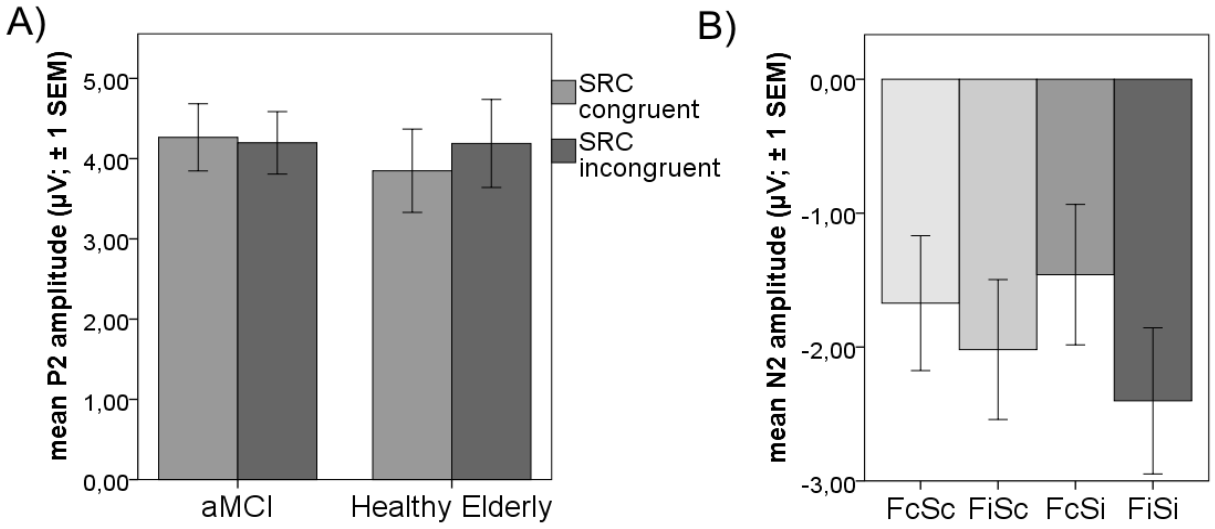

Figure 14 A) Illustration of the mean P2 amplitude in congruent and incongruent SRC trials in elderly with aMCI and healthy controls. Healthy elderly exhibit increased SRC induced P2 amplitude modulation in comparison to aMCI participants. B) Illustration of the mean N2 amplitude. The N2 amplitude is particularly enhanced in trials with two sources of conflict (FiSi), while the effects of the single conflict conditions (FiSc and FcSi) are less pronounced.

4.3.4 fMRI results

The analysis of the fMRI data included the contrasts of the incongruent Flanker [FiSc], incongruent SRC [FcSi], and the double incongruence [FiSi] condition against the double congruence condition [FcSc]. These contrasts were calculated for every participant of each group and entered into a between group analysis. The results are illustrated in *Table 5*, *Table 6* and *Figure 15*.

Single Flanker conflict trials elicited increased activation in the PFC including the MFG and the cingulate gyrus. In addition, elderly also recruited the IPL, the precuneus and the cuneus in incongruent Flanker trials. In the aMCI group, significant signal increase was detected in the IFG and the precuneus (extending to the cuneus). Conjunction analysis confirmed that the precuneus and cuneus were commonly activated by both groups. In contrast, interaction analysis revealed that the IPL was specifically activated by healthy elderly.

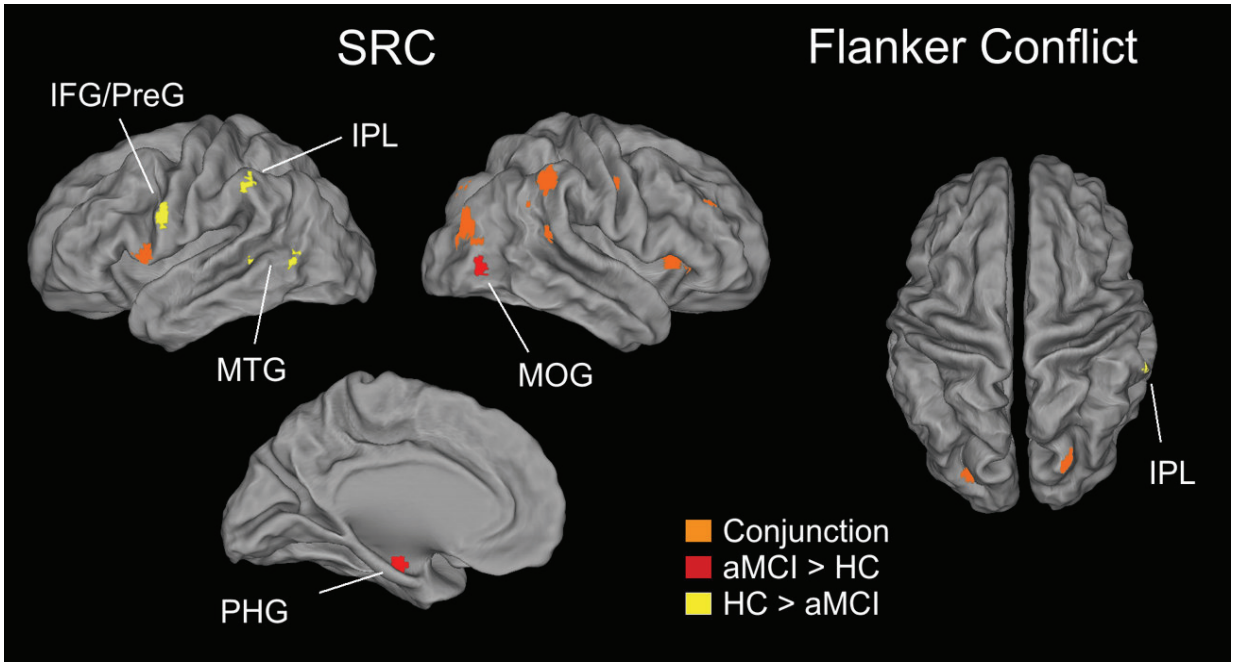

Figure 15 Illustration of different activation patterns for the SRC and the Flanker conflict. Red and yellow areas indicate activation differences between elderly with aMCI and healthy (thresholded at p < .005; k=15). Orange areas indicate common areas of activation obtained from conjunction analysis (thresholded at p < .005 (uncorrected), k=15).

Healthy elderly showed increased activation in the area of the IFG, the PreCG and the insula in response to the single SRC condition. Furthermore, significant signal increase was detected in posterior regions including the IPL and the supramarginal gyrus, the precuneus, the cuneus, the paracentral lobule, the MTG, the STG, and the FFG and lingual gyrus. Indiviuals with aMCI also recruited a network of frontal, parietal and temporal regions including the MFG, the IPL, the insula, the STG, the MTG, the FFG and lingual gyrus and PHG, but also the MOG. Common activation was identified by a conjunction analysis in the MFG, in clusters located around the IFG, the PreCG and insula, in the IPL, the precuneus and the MTG. Increased activation in healthy elderly was detected in the IPL, the IFG and the MTG by the interaction analysis. In contrast, participants with aMCI showed increased activation of the medial temporal lobe (including the PHG and the hippocampus) and the MOG.

The double conflict condition triggered increased activation of the IPL in healthy elderly. Elderly with aMCI recruited the cingulate gyrus, the SFG, the MTG, the lingual gyrus and the cerebellum in this condition. The conjunction analysis revealed no common activation clusters in double conflict trials.

Table 5 Peak activations derived from a conjunction analysis (intermediate null hypothesis, p < .005 (uncorrected), k = 15) and an interaction analysis (p < .005, uncorrected, k = 15) of the Flanker [fisc > fcsc], SRC [fcsi > fcsc], and double conflict (Flanker + SRC) [fisi > fcsc] contrasts for elderly with and without aMCI. In addition, group contrasts thresholded at p < .005 (uncorrected) of the respective groups were used as an inclusive mask. Abbreviations; x, y, z = MNI coordinates of peak activations; SRC = stimulus-response conflict.

	Conjunction			Interaction		
				Healthy Elderly > aMCI		
	x y z	t-value	Cluster-size	x y z	t-value	Cluster-size
Flanker Conflict						
Cuneus	-22 -80 21	3.70	44			
Precuneus	22 -78 40	3.68	76			
Inferior Parietal Lobe				64 -38 43	3.64	27
SRC						
Middle Frontal Gyrus	38 38 35	3.69	29			
Inferior Frontal Gyrus	-40 22 5	3.41	44	-60 4 27	4.67	33
Precentral Gyrus	-52 14 5	3.96	43			
	44 -10 35	3.72	40			
Insula	34 10 8	3.64	21			
	30 22 8	4.97	85			
Middle Temporal Gyrus	40 -76 21	4.31	104	-52 -42 0	3.35	20
				-58 -62 3	3.48	26
Inferior Parietal Lobe	52 -38 43	4.15	233	-56 -40 45	3.86	22
Precuneus	20 -70 48	3.69	75			
				aMCI > Healthy Elderly		
				x y z	t-value	Cluster-size
Parahippocampal Gyrus				-26 -14 -19	3.86	29
Middle Occipital Gyrus				40 -70 3	3.94	41
Flanker Conflict + SRC						
Cingulate Gyrus				14 -4 35	3.42	20
Superior Frontal Gyrus				32 26 53	3.54	24
Middle Temporal Gyrus				66 -38 -3	4.93	30
				58 -68 5	3.79	50
Lingual Gyrus				-18 -68 3	3.46	24
Posterior Cingulate				22 -50 16	4.08	87
Cerebellum Anterior Lobe				16 -56 -35	4.18	28

Table 6 Peak activations for the Flanker [FiSc > FcSc], SRC [FcSi > FcSc], and double conflict (Flanker + SRC) [fisi > fcsc] contrasts, for elderly participants with and without aMCI. All reported regions are significant at p < .001 (uncorrected) with a spatial extent threshold of k = 15. Abbreviations: x, y, z = MNI coordinates of peak activations.

	Healthy Elderly			aMCI		
	x y z	t-value	Cluster-size	x y z	t-value	Cluster-size
Flanker Conflict						
Middle Frontal Gyrus	52 32 29	5.42	61			
	36 -2 48	4.43	15			
Inferior Frontal Gyrus				-44 22 -3	4.52	21
Cingulate Gyrus	-10 16 40	4.66	28			
Inferior Parietal Lobule	62 -32 27	4.58	63			
Precuneus	-14 -58 50	4.59	56	-16 -70 19	4.02	41
	22 -80 43	4.83	76	34 -68 32	3.96	16
	14 -60 51	4.15	32			
Cuneus	-22 -82 21	4.43	35			
SRC						
Middle Frontal Gyrus				36 32 32	4.31	46
Inferior Frontal Gyrus/	-60 2 24	4.54	18			
Precentral Gyrus	-52 12 8	5.90	116			
	-48 -2 40	5.52	53			
	-40 28 0	4.44	32			
Insula	30 22 8	4.97	45	32 24 8	5.84	47
Postcentral Gyrus	-60 -20 32	4.33	20			
Inferior Parietal Lobule/	58 -46 35	5.05	315	56 -42 21	4.36	87
Supramarginal Gyrus	-58 -40 43	5.90	269			
Precuneus	20 -74 35	4.54	87			
	-22 -68 37	4.16	30			
	-10 -58 51	5.21	90			
	14 -58 51	4.83	71			
Paracentral Lobule	4 -35 51	4.32	35			
Cuneus	18 -90 19	4.77	42			
	-10 -90 29	4.92	31			
Superior Temporal Gyrus				-36 -36 13	5.92	134
				40 -32 11	4.16	16
Middle Temporal Gyrus	38 -76 21	4.95	63	40 -74 24	4.48	41
	-56 -60 3	5.99	218			
Fusiform Gyrus/	20 -64 -16	4.39	16	-20 -64 3	5.92	168
Lingual Gyrus				-4 -64 3	4.50	28
Parahippocampal Gyrus				-26 -14 -16	4.07	18
Middle Occipital Gyrus				46 -68 3	6.03	207

Table 6 (continued)

	Healthy Elderly				aMCI			
	x	y	z	t-value	Cluster-size	x	y	z	t-value	Cluster-size
Flanker Conflict + SRC										
Inferior Parietal Lobule	56	-36	43	4.57	64					
Superior Frontal Gyrus						24	52	41	4.42	19
						22	12	48	4.35	98
Medial Frontal Gyrus						8	32	37	4.46	72
Precuneus						28	-66	41	4.11	34
Lingual Gyrus						-16	-88	-11	4.80	17
Inferior Occipital Gyrus						-46	-82	-5	3.93	17
MiddleOccipital Gyrus						-42	-74	-13	4.52	28

4.4. Discussion

The present study investigated interference processing using ERP and fMRI in a combined SRC and Flanker conflict task in male elderly with and without aMCI. Though no group difference were evident regarding RTs and error rates, ERP and fMRI results indicate that in particular, the neural correlates of SRC processing are modified in elderly with aMCI. The fMRI analyses yielded a common fronto-parietal activation pattern associated with the SRC. However, the comparison between both groups demonstrated that healthy elderly exhibited increased activation in frontal and parietal areas while elderly with aMCI additionally recruited the PHG and the MOG. Furthermore, enhanced P2 amplitudes in response to incongruent SRC trials were only detectable in healthy controls. Taken together, these results suggest that compensatory mechanisms that are frequently detected in healthy ageing seem to become less efficient in patients with aMCI.

Flanker Conflict

The analysis of the behavioral data yielded a significant delay of RTs on incongruent Flanker trials, while error rates were unaffected by the Flanker conflict in both groups. These results are in line with previous reports of Flanker processing in different age groups. However, in contrast to previous studies (Wang et al., 2013; Wylie et al., 2007) there were no differences of behavioral performance between elderly with and without aMCI in the present study.

Flanker incongruent trials were furthermore associated with an increased P2 and a decreased P3 amplitude when compared to congruent trials, indicating that early and late stages of information processing may be affected by the Flanker conflict. These findings correspond with previous ERP studies of conflict resolution in healthy young and elderly adults (Gajewski et al., 2008; West et al., 2004). In the present study, these amplitude effects were also detectable in elderly with aMCI. The effect of the Flanker conflict on the ERPs did not differ between both groups for all analyzed time windows. Furthermore, there were no group differences of the mean amplitudes in any of the investigated ERP components. This result does not confirm previous reports of increased N2 and decreased P3 amplitudes in aMCI in conflict (Wang et al., 2013) and other cognitive tasks compared to healthy elderly, but may rather suggest that the resolution of the Flanker conflict is not altered in individuals with aMCI.

A conjunction analysis of the fMRI data illustrated that both groups exhibit increased activation of the cuneus and the precuneus in both hemispheres in response to the Flanker conflict. The single group analyses further demonstrated that participants with aMCI also activated the IFG, while healthy elderly additionally recruited the MFG, the cingulate gyrus and the IPL. However, an interaction analysis showed activation differences between both groups only in the IPL. The activation pattern of both groups correspond with existing reports on neural networks of conflict processing: The detection and evaluation of conflict stimuli is associated with activation of the cingulate cortex and the IFG, and the implementation of inhibition causes increased activity in prefrontal areas comprising the MFG and IFG. Furthermore, parietal areas such as the cuneus, the precuneus and the IPL are recruited during tasks that require focusing of attention and processing of spatial information. The functional data of the present study may denote that patients with aMCI and elderly controls recruit common as well as distinct neural networks to process incongruent Flanker information. These results do not substantiate findings of markedly increased activation in aMCI patients as found in a Stroop task study (Li et al., 2009).

Altogether, the present ERP and fMRI results pattern suggests that Flanker conflict processing is overall equivalent in elderly males with and without aMCI. Though both groups partly recruit distinct areas during the Flanker conflict task (left IFG vs. right MFG and cingulate gyrus), these regions are known to support similar cognitive mechanisms associated with conflict processing. Additionally, the ERP results indicate that the temporal characteristics of the Flanker conflict do not differ between the groups.

SRC

The incongruent SRC condition induced a reduction of the P3 amplitude in both groups. This result is in line with other studies that detected a reduction of the P3 amplitude in young and healthy elderly adults in conditions that pose high demands to cognitive control mechanisms. Experiment 2 of the present thesis demonstrated that the SRC-induced modulation of the P3 amplitude is more pronounced in healthy elderly than in young controls. By contrast, past ERP studies provide inconsistent results about alterations of the P3 amplitude in elderly with aMCI. In accordance with a study by Cespon et al. (2014), the present data suggest that the aMCI is not associated with a decreased P3 amplitude in the context of SRC processing. Thus, the implementation of cognitive mechanisms indexed by the P3 such as context updating seems to be equivalent in both groups. In contrast, the ERP analysis hints at group differences in the early P2 related time window. Only healthy elderly exhibited an amplitude increase in response

to incongruent SRC trials while the P2 component remained unaffected by the SRC in males with aMCI. In the literature, there is evidence that the P2 component is altered in elderly with aMCI in an emotional face recognition task (Schefter et al. 2013). The importance of early processing stages for the differentiation between both groups is furthermore substantiated by studies that found differences of the MMN induced by visual and auditory task designs between elderly with and without aMCI (Tales et al. (2008). The comparison of young and healthy elderly participants in Experiment 1 revealed that elderly adults elicit enhanced SRC induced modulation of the P2 amplitude compared to young adults while the influence of the Flanker conflict was equivalent in both groups. The enhanced P2 amplitude possibly reflects a compensatory recruitment of neural resources to cope with the more difficult incongruent condition. The decrease of this modulation in elderly with aMCI might indicate that this compensatory mechanism is diminished in pathological ageing, possibly due to less cognitive capacities. Since the P2 component is associated with stimulus evaluation (Potts, 2004; Riis et al., 2009), the classification of stimuli with regard to their task relevance is possibly less efficient in aMCI-subjects.

A conjunction analysis revealed that fMRI clusters in frontal areas such as the IFG, MFG and PreCG and parietal (IPL) and temporal (MTG) areas were commonly activated during SRC processing by elderly with and without aMCI. These areas correspond with the results of other conflict task studies with young and elderly subjects. However, there was also group specific activation as indicated by an interaction analysis: Healthy elderly showed increased activation of the IFG, the MTG and the IPL, while participants with aMCI additionally recruited areas of the PHG and the MOG. The increased activation of parietal and frontal areas is frequently reported in healthy elderly when compared to young controls across different tasks. Different theories of ageing argue that this increased activation serves as a compensatory mechanism to maintain high performance despite age-related alterations of the brain such as shrinkage of brain tissue, changes of transmitter systems etc. Apparently, this mechanism is less pronounced in individuals with aMCI. In contrast, they elicit increased activation of occipitotemporal regions. Interestingly, while healthy controls intensify the activation of areas that are linked to inhibition and spatial processing, aMCI is associated with additional recruitment of areas that are not specifically linked to interference control but rather support basic visual processes and memory functions. Similar results were obtained by Kaufmann et al. (2008) with a Stroop task. There are different explanations for this result. Elderly with aMCI possibly exhibit a distinct functional organization of the brain or employ a modified processing strategy that places more emphasis on the described functions. Another possibility is that the compensatory mechanism

is less efficient in the context of pathological ageing, so that instead of higher levels of activity of task-relevant brain regions, overrecruitment becomes less specific and extends to task-irrelevant networks. Correspondingly, there are other studies that detected increased but unspecific activation elderly with aMCI (Bokde et al., 2008). Another explanation especially focuses on the increased activation located in the PHG and the hippocampus. Several studies evidenced higher activity in the hippocampal area in aMCI during different memory tasks. This increase is frequently considered to represent a compensatory mechanism for the structural decline of this area. However, Bakker et al. (2012) reduced hippocampal activity in participants with aMCI by means of an antiepileptic drug (levetiracetam) and found that the activity reduction improved performance in a three choice memory task. This result suggests that the increased activation of the hippocampus is not related to beneficial mechanisms but rather interferes with efficient cognitive functioning. The present data may indicate that the increased hippocampal activation is not only restricted to memory tasks but also emerges in situations of high demand of control mechanisms. However, based on the present analysis it cannot be determined whether the activation increase of the PHG and the hippocampus has a beneficial or a detrimental effect on performance in the context of conflict processing.

In summary, neural correlates of SRC processing seem to be modified in aMCI. Despite common activation of prefrontal and parietal areas, neural recruitment seems to be less specific in aMCI, possibly indicating a gradual breakdown of compensatory mechanisms. Furthermore, the ERP data suggest that these compensatory mechanism are possibly related to early stages of stimulus evaluation.

Flanker conflict + SRC

The present ERP data pattern implies that the N2 amplitude is increased by incongruent Flanker trials only when there is a concurrent SRC conflict and vice versa, while both conflict types did not affect the N2 amplitude in single conflict trials. This finding contradicts the results of Experiment 2 of this thesis that points to a Flanker conflict induced modulation of the N2 component without an interaction of both conflict types. Likewise, a double conflict study by Frühholz et al. (2011) also found N2 amplitude differences between congruent and incongruent trials of the Flanker conflict but not of the SRC task. This conflicting result possibly grounds on inter-individual differences of the interaction of the SRC and Flanker conflict in elderly adults. The interaction between age groups indicates that the processing of both conflict types is based on (partially) common cognitive operations. Ageing may be accompanied by limited cognitive resources or decreased functional specificity of different cognitive mechanisms.

Thus, the simultaneous presence of two conflict sources possibly exceeds the ability of some elderly adults to process both conflict types independently. However, the fact that this interaction was not observed in the analysis of the whole group of healthy elderly (see Experiment 2) indicates that this effect is not consistently linked to healthy ageing. Moreover, these results are probably biased by the small sample size or gender-related effects. Thus, further studies with a larger sample size are needed to clarify the interaction of the SRC and the Flanker conflict with regard to the N2 amplitude in elderly with and without aMCI.

The fMRI analysis of the double conflict condition yielded increased activation of the IPL in the right hemisphere in healthy elderly. Signal increase in this area was also detected in the single conflict contrasts and indicates the increased implementation of spatial processing and attentional biasing of relevant and irrelevant information. With regard to the results of the single conflict conditions and of the double incongruence condition of the whole group analysis (see Experiment 1) it is possible that inter-individual activation differences undermined within-group effects due to the small sample size. The analysis of the whole group of healthy elderly illustrated that double conflict trials triggered increased activation in various parietal and prefrontal regions such as IFG, MFG, cingulate gyrus, and precuneus. These regions were also recruited in the single conflict trials. By contrast, elderly with aMCI elicited activation of the MOG, the MFG and SFG and of the precuneus in the double conflict task. This activation pattern corresponds with the results of the single conflict contrasts and suggests that elderly with aMCI employ similar cognitive mechanisms for the processing of single and double conflict trials.

Taken together, these data indicate that the neural mechanisms supporting Flanker conflict resolution are equivalent in elderly with and without aMCI. In contrast, the neural correlates of SRC processing are modified in aMCI, possibly due to less efficient compensatory mechanisms.

5. General Discussion

The aim of the present thesis was to investigate the effects of healthy and pathological ageing on different components of interference control. Therefore, a combined SRC and Flanker conflict task was employed in three experiments including young adults, healthy elderly and elderly with aMCI. In addition, the recording of ERP and fMRI data provided information about the neural mechanisms underlying both conflict types in the respective groups. The data obtained from the three experiments indicate that different components of interference control represented by the SRC and the Flanker conflict are distinctively modified by healthy and pathological ageing. The first evidence is provided by the analysis of RT data that revealed that the SRC effect is increased in healthy elderly in comparison to young adults while the Flanker conflict does not differ between both groups. Conflict-specific ageing effects were furthermore observed in the ERP and fMRI data. The Flanker conflict elicited similar activation patterns in young and elderly adults, whereas SRC processing was associated with marked differences of neural processing in both groups. In addition, ERP results revealed that the SRC and the Flanker conflict differentially affected early processing stages in healthy elderly. The comparison of elderly with and without aMCI suggests that aMCI is associated with a modified activation pattern and alterations of early processing stages in the context of the SRC. By contrast, neural correlates of the Flanker conflict are comparable in both groups.

These results raise the question whether the conflict-specific neural correlates obtained from ERP and fMRI analyses reflect corresponding neural mechanisms. More precisely, is e.g. the additional recruitment of the IFG and IPL in healthy elderly functionally connected to the increased modulation of the P2 amplitude? Or do these correlates reflect independent neural mechanisms? Another question focuses on the functional role of the neural alterations associated with healthy and pathological ageing and how these differences can be embedded into different ageing theories. These questions cannot be definitely answered without a further analysis combining fMRI, EEG and behavioral data, however, the following sections provide a theoretical approach to integrate the different findings of the present thesis and the literature on healthy and pathological ageing. Furthermore, limitations of the present thesis and the outlook to future research are discussed at the end of this chapter.

5. 1. Integration of the ERP and fMRI results

5.1.1. SRC Task

fMRI analysis revealed that SRC processing is associated with qualitatively different activation patterns in elderly and young adults. Incongruent SRC trials induced increased activation of the IPL and the IFG specifically in elderly. These areas are associated with inhibition and evaluation processes respectively spatial attention and top-down modulation Aron et al., 2003a; Hampshire et al., 2010; Chikazoe et al., 2007; Yantis et al., 2002; Hopfinger et al., 2000). In contrast, young adults exhibit clusters of deactivation in response to incongruent SRC trials. These results suggest that elderly and young controls implement qualitatively different processing strategies: while elderly rely on the inhibition of incorrect response activation and attentional modulation of the relevant and irrelevant stimulus feature representation, the SRC effect is possibly based on facilitation effects in young adults. ERP analysis also revealed group differences in SRC processing: Elderly adults exhibit a P2 amplitude increase in the incongruent SRC condition while the P2 was unaffected by the SRC manipulation in young controls. Furthermore, the decrease of the P3 amplitude in response to incongruent SRC trials was more pronounced in elderly than in young participants. Elevated P2 amplitudes are detected in conditions with low discriminability between single stimulus features and also in conditions with a mismatch of the current stimulus with a standard stimulus set (Kim et al., 2008). Thus, early evaluative mechanisms are possibly enhanced in elderly to ensure the correct identification of relevant and irrelevant input and to promote the processing of the mismatch of spatial and color information in incongruent SRC trials. The augmented modulation of the P3 possibly reflects a higher need of updating context information and a stronger demand for attentional resources in conflict trials in elderly (Donchin and Coles, 1988; Polich and Heine, 1996). The frontal topography of the P2 suggests that age-specific differences of the modulation of this component are mediated by regions of the PFC. In contrast, the parietal topography of the P3 component possibly indicates that regions in the parietal cortex contribute to the modulation of the P3 amplitude. Thus, the increased activation of the IFG in healthy elderly is possibly associated with a rather early stage of conflict processing represented by the P2 while the additional recruitment of the IPL is probably linked to later stages of conflict resolution indicated by the P3. Indeed, various source analysis studies demonstrated that the IPL and adjacent regions are involved in the generation of the P3 (Bledowski et al., 2004; Moores et al., 2003; Menon et al., 1997; Mulert et al., 2004). Further evidence is provided by Verleger and colleagues (1994) who demonstrated that the P3 (induced

by standard visual stimuli) is diminished in patients with lesions of the parietal cortex and the temporo-parietal junction. In contrast, such alterations were not observed after frontal lesions. Interestingly, this study also revealed that patients with frontal lesions of the left hemisphere showed a marked increase of an early positive component peaking at 150 ms (P150) that was not detectable in patients with lesions of the right frontal cortex or posterior brain regions. Though the P2 in the present data showed a slightly later peak, both components (P2 and P150) refer to early stages of visual processing and thus probably reflect similar cognitive mechanisms. Studies investigating neural generators of the P2 in healthy participants are sparse. Potts (2004) detected that the IFG is involved in the neural generation of the P2 in a visual oddball task. However, the P2 time window (220-316 ms) differed from the P2 epoch in the present ERP analysis (170-210 ms in elderly). Taken together, there is considerable evidence that the IPL is involved in P3 generation, whereas the neural origins of the P2 are less clear. With regard to the ageing effects found in the present data, it thus can be assumed that the additional recruitment of the IPL in elderly is possibly related to the increased modulation of the P3 amplitude. Furthermore, The P3 and the IPL are both associated with attentional control mechanisms. In contrast, it is unclear whether the increased modulation of the P2 in elderly can be associated with the IFG, the IPL, both or none of them. There are hints that neural generators of the P2 might be located in the (left) IFG. Furthermore, the P2 and the IFG are associated with corresponding cognitive mechanisms such as stimulus evaluation with regard to task relevancy.

5.1.2. Flanker Task

In contrast to the SRC task, the Flanker conflict elicited similar activation patterns in young and elderly participants. Both groups recruited a common “core network” including the basal ganglia, cingulate gyrus and the MOG. Based on these data it can be assumed that Flanker conflict processing does not change substantially with advanced age but rather undergoes slight modifications. The ERP analysis yielded that the P2 and N2 amplitudes were increased by the Flanker conflict in both groups, however, the N2 amplitude modulation was stronger in young adults. Additionally, the Flanker conflict-related modulation of the P3 amplitude was more pronounced in elderly than in young subjects. Various studies found that the generators of the N2 component are located in the medial wall of the PFC. Thus, in the present data the Flanker conflict associated increase of the N2 amplitude is possibly linked to the increased activation of the cingulate gyrus. The modulation of the P2 and the P3 amplitude were also reported for the

SRC and associated with the increased activation of the IPL and IFG in elderly participants. However, fMRI data did not reveal age-related activation differences in these regions during Flanker task processing. Thus, the modulation of the P3 and P2 amplitude might be mediated by distinctive areas in the SRC and Flanker conflict tasks. The recruitment of other parietal regions (Precuneus and SPL) in response to the Flanker conflict in elderly adults possibly accounts for the age-related increase of P3 amplitude modulation. Indeed, these region were found to be involved in the generation of the P3 as well (Mulert et al., 2004). The comparison of elderly with and without aMCI yielded increased activation in the precuneus and prefrontal areas (cingulate gyrus and MFG in healthy elderly, IFG in elderly with aMCI). Furthermore, in both groups the Flanker conflict increased the P2 and decreased the P3 amplitude.

Taken together, the comparison of the fMRI and EEG data suggests that Flanker effects on early processing stages are mediated by activation of the cingulate gyrus, while congruence effects in later stages are linked to the precuneus and SPL. In contrast, later stages of SRC processing are probably related to the IPL. Early processing mechanisms of the SRC are probably critical for the increased susceptibility of the SRC to effects of (healthy and pathological) ageing. There is evidence, that the left IFG is associated with these mechanisms, however, results in this field are very sparse.

5.2. Functional role of the neural correlates associated with healthy and pathological ageing

The second question refers to the functional role of the neural alterations (particularly of SRC processing) associated with healthy and pathological ageing. Various studies found that ageing affects the inhibition of distractor stimuli, while target related processes remain relatively unaffected (de Fockert et al., 2009; West and Alain, 2000; Wascher et al., 2012). Moreover, the inhibition of distractors that are confounded with the target stimulus (as found in the SRC task of the present task design) is particularly difficult for elderly individuals (Proctor et al., 2005). Thus, the SRC-related ERP and fMRI results probably reflect cognitive mechanisms that are critically linked to this difficulty. The present results might reflect age-related deficiencies of the neural dynamics of SRC processing or they represent compensatory mechanisms that try to counteract the increased efforts of SRC resolution in elderly. Riis and colleagues (2009) also detect an increase of the P2 amplitude modulation in elderly in response to novel stimuli. They argued that if this increase indicates the cognitive decline associated with ageing, then

modulation of the P2 should be particularly enhanced in elderly participants with lower scores in neuropsychological tests. However, their comparison of low and high performing elderly yielded no significant differences in the P2 amplitude. The authors thus concluded, that the age-related modification of the P2 amplitude does not reflect the age-related decline of the mechanisms indexed by the P2. Investigations focusing on the effects of extended activation in elderly yield conflicting results. Various studies propose that additional neural recruitment is particularly pronounced in high performing elderly (Reuter-Lorenz et al., 2000; Rosen et al., 2002; Grady et al., 2002). In contrast, Meinzer and colleagues (2013) demonstrated that activity reduction in prefrontal cortices induced by anodal transcranial direct stimulation, improved performance scores in a semantic word retrieval task in elderly. With regard to the present data, the comparison of elderly with and without aMCI rather points to the compensatory function of the additional activation and the increased amplitude modulation observed in healthy elderly, because these alterations do not continuously evolve with declining cognitive status but rather seem to regress in individuals with aMCI. If these neural correlates reflected age-related deficits in interference control, the results of the present thesis would suggest an improvement of neural processing of the SRC task in aMCI. In consideration of the studies indicating a decline in interference control in aMCI this seems rather unlikely. Thus, the comparison of elderly with and without aMCI argues in favor of the compensatory role of the neural response observed in healthy elderly. Accordingly, in the transition of healthy to pathological ageing compensatory mechanisms seem to become less efficient. Nevertheless this "decompensation" has no detrimental effects on behavioral performance – at least in the stage of aMCI. Importantly, this transition of neural compensation mechanisms seems to be specific for different functions. In contrast to the processing of the SRC, neural correlates of the Flanker conflict were only slightly modified in healthy elderly and individuals with aMCI. Thus, compensation and decompensation mechanisms associated with Flanker conflict processing are possibly less pronounced or evolve in later stages of cognitive decline.

There are probably multiple reasons for the decompensation observed in elderly with aMCI. Baltes and Lindenberger (1997) proposed that ageing is accompanied by the functional dedifferentiation of neural processing. Due to the accumulation of pathological processes in the brain of elderly with progressed cognitive decline, dedifferentiation is possibly particularly pronounced and thus decreases specificity of activation in response to the SRC. Hence, theoretical approaches such as the PASA and the HAROLD theory that highlight the compensatory effect of increased activation in elderly cannot be transferred to pathological ageing without any limitations.

5.3. Limitations and future research

There are several limitations with regard to the analysis and interpretation of the present data. One critical factor is the small sample size of the aMCI group. Small sample sizes are associated with a decreased statistical power and thus a decreased probability to detect significant effects. Hence, potential differences of SRC and Flanker conflict processing between elderly with aMCI and healthy controls were possibly not recognized due to the lack of statistical power. Small sample sizes additionally increase the risk of sampling errors. Furthermore, only male participants were included for the comparison of healthy and pathological ageing. Thus, the results are possibly biased by gender specific effects of ageing and conflict processing and cannot be generalized to a broader population. Thus, the investigation of interference control in aMCI represents an exploratory approach that helps to generate hypotheses for future investigations of interference control in the context of pathological ageing. Moreover, the sample size was too small to subdivide the participants into a single and multiple domain group. This comparison could provide further information about the transition of compensatory effects in pathological ageing in dependence of the severity of cognitive deficits. Furthermore, due to the cross-sectional design of the present studies cohort effects cannot be ruled out.

Another limitation of the present thesis is that the integration of different data sets was based on theoretical assumptions. In future studies different statistical approaches could be uses to combine fMRI, ERP, and behavioral data. Various source analysis techniques can provide information about the interaction of spatial and temporal characteristics of neural processing. Furthermore, the functional role of neural alterations associated with healthy and pathological ageing can be examined with correlation analyses of performances scores and neural correlates. Finally, the integration of memory scores and neural indicators of interference control can provide information about how and to which amount interference control contributes to memory dysfunction in healthy and pathological ageing.

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I am very grateful to Daniela Galashan, Julia Siemann, Charlotte Herzmann, Stephan Miedl, Sascha Clamer, Sascha Frühholz, David Berron, Barbara Muntz, Tim Reeß, Daniel Wiswede, Peter Erhard, Maren Prass, and many more who always helped me out with professional advice, moral support, and interesting discussions. I would also like to thank Roman Konstantinov and Melanie Löbe for their help with data acquisition.

Special thanks go to my family, in particular to my parents Rosa and Paul Korsch, but also to my friends for their unconditional support in any situation.

Finally, I want to thank the volunteers for their participation in the experiments.

Appendix

Appendix A (1): General information about the study procedure

Probandeninformation

Die Abteilung für Neuropsychologie und Verhaltensneurobiologie (Prof. Dr.med. Dr.phil. Herrmann) des Zentrums für Kognitionswissenschaften (ZKW) an der Universität Bremen führt eine Studie zu den *neuronalen Grundlagen der Interferenzkontrolle in Abhängigkeit von Gedächtnisleistungen in verschiedenen Altersgruppen* durch.

Was ist Interferenzkontrolle?

In unserer Umwelt sind wir tagtäglich einer Fülle von Eindrücken ausgesetzt. Diese Fülle kann dazu führen, dass wir uns durch unwichtige Eindrücke ablenken lassen. So ist es z.B. besonders schwierig sich auf etwas zu konzentrieren, wenn man von störenden Reizen umgeben ist (z.B. Lärm). Interferenzkontrolle meint die Fähigkeit solche irrelevanten Störreize ausblenden zu können um sich auf relevante Reize zu konzentrieren.

Was ist das Ziel der Studie?

Altern ist mit bestimmten geistigen Veränderungen assoziiert. Uns interessiert, ob sich die Fähigkeit der Interferenzkontrolle im Alter verändert und inwieweit das Gehirn solche Veränderungen kompensieren kann. Weiterhin möchten wir untersuchen, ob alterstypische Beeinträchtigungen – z. B. des Gedächtnisses – mit Veränderungen der Interferenzkontrolle zusammenhängen.

Wie läuft die Studie ab?

Die Studie setzt sich aus drei Teilen zusammen, die an drei verschiedenen Terminen durchgeführt werden sollen:

1. *Neuropsychologische Untersuchung:* In der neuropsychologischen Untersuchung werden einige Tests durchgeführt, die uns helfen sollen Ihre kognitiven Leistungen (z. B. Gedächtnis, Aufmerksamkeit,...) einzuschätzen. Neben solchen Tests gibt es auch einige Fragebögen.
   Diese Informationen sind für uns wichtig, damit wir wissen inwieweit wir einzelne Teilnehmer miteinander vergleichen und die Ergebnisse der Studie letztendlich interpretieren können.

   Dieser Teil der Studie wird teilweise am Computer und teilweise mit Stift und Papier durchgeführt und dauert ca. 60 Minuten.

Appendix A (2): General information about the study procedure

2. *EEG-Untersuchung (**E**lektro**e**nzephalo**g**ramm):* Bei der EEG-Untersuchung sitzen Sie vor einem Bildschirm, auf dem Sie verschiedene Hinweisreize sehen, auf die Sie entsprechend einer bestimmten Aufgabe reagieren sollen. Auf Ihrem Kopf werden mit Hilfe einer Kappe 64 Elektroden platziert, die mit einem Gel präpariert werden. Die Elektroden und das Gel lassen sich ohne bleibende Rückstände wieder entfernen. Diese Methode ist nicht invasiv und frei von Risiken.
   Wir führen die EEG-Messung durch um zu erfahren wie Interferenzkontrolle im Gehirn verarbeitet wird. Mit Hilfe des EEGs kann man messen ***wann*** etwas im Gehirn passiert.

   Diese Messung dauert insgesamt ungefähr 90 Minuten.

3. *fMRT-Untersuchung (**f**untkionelle **M**agnet**r**esonanz**t**omographie):* Bei dieser Messung liegen Sie (Rückenlage) in einem Kernspintomographen und sehen über eine Spiegelvorrichtung verschiedene Hinweisreize, auf die Sie reagieren sollen. Um an dieser Messung teilnehmen zu können, müssen Sie einige Voraussetzungen erfüllen (z. B. keine magnetisierbaren Gegenstände am Körper tragen), die wir im Vorfeld sorgfältig mit Ihnen abklären werden.
   Auch diese Messung soll uns Aufschluss darüber geben, wie Interferenzkontrolle im Gehirn verarbeitet wird. Mit Hilfe der fMRT kann man messen ***wo*** etwas im Gehirn passiert.

   Diese Messung dauert ca. 45 Minuten.

Schutz der Probanden

Sie erhalten zu jeder Messung bei den einzelnen Terminen eine ausführliche Aufklärung.
Die Messungen werden von geschultem Fachpersonal durchgeführt.
Sie können die Teilnahme an dem Experiment zu jedem Zeitpunkt und ohne Angabe von Gründen abbrechen.Die Daten aller drei Messungen werden pseudonymisiert gespeichert, so dass für keinen außer der Untersuchungsleitung ein Rückschluss auf Ihre Person möglich ist. Die Daten werden nur für dieses Projekt und im Rahmen wissenschaftlicher Veröffentlichung genutzt.

Wir freuen uns über Ihre Unterstützung bei diesem Projekt.

Ansprechpartnerin

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Appendix B(1): Information on EEG measurement

Informationsblatt für Probanden

Sehr geehrte Probandin, sehr geehrter Proband,

vielen Dank für Ihr Interesse, an unserer Studie teilzunehmen, in der wir die Arbeit des Gehirns bei der Verarbeitung von Interferenzkontrolle untersuchen möchten. Wir möchten Sie zunächst über den Ablauf informieren, um Ihnen einen Überblick über die geplanten Messungen zu ermöglichen und Ihnen das Ziel der Untersuchung zu erklären.

Wir bitten Sie im Falle Ihrer Teilnahme um eine aktive Mitarbeit bei den nachfolgend erläuterten Untersuchungen. Sie haben das Recht, jederzeit ohne Angabe von Gründen und ohne persönlichen Nachteil die Teilnahme an der Untersuchung abzulehnen oder während der Messung abzubrechen.

Ziele und Ablauf der Untersuchung

Die Studie soll die Verarbeitung von Interferenzkontrolle in Abhängigkeit von verschiedenen kognitiven Alterungsprozessen untersuchen. Zu diesem Zweck werden Ihnen bei der Untersuchung wiederholt visuelle Reize gezeigt, die Sie entsprechend einer vorher vom Versuchsleiter erklärten Aufgabe bearbeiten sollen. Während dieser Tätigkeit wird Ihre Hirnaktivität gemessen. Die Untersuchungen werden mit Hilfe der Elektroenzephalographie (kurz EEG) durchgeführt, die Messungen der Nervenzell-Aktivität im Gehirn ohne Eingriff, schmerzfrei und *ohne zusätzliche Gabe von Medikamenten* ermöglicht.

Beschreibung des Elektroenzephalogramms (EEG)

Aufgrund der Aktivität der Nervenzellen lässt sich an der Kopfoberfläche fortlaufend eine elektrische Spannung messen – das Elektroenzephalogramm (EEG). Für die EEG-Messung müssen an verschiedenen Stellen des Kopfes Elektroden platziert werden, die eine Verbindung zwischen Kopfoberfläche und Messgerät herstellen.

Die Elektroden bestehen aus Silber/Silberchlorid, Zinn oder Gold. Zur Verbesserung der Leitfähigkeit wird eine Paste verwendet, die im Wesentlichen aus Wasser, Kochsalz und Verdickungsmittel besteht. Um zwischen Haut und Elektrode einen hinreichend guten Kontakt herzustellen, werden die Elektroden an einer speziellen Haube, ähnlich einer Badekappe, fixiert.

Ablauf der EEG-Untersuchung

Vor der Untersuchung werden Sie vom Untersuchungsleiter ausführlich über die für den Tag geplanten Messungen und Ziele informiert. Die Untersuchung dauert ca. 90 Minuten. Im Verlauf der Untersuchung werden Sie vom Untersucher jederzeit gehört, so dass Sie sich jederzeit nach außen bemerkbar machen können.

Während der Untersuchung sitzen Sie auf einem Untersuchungsstuhl. Um Störungen der Messung zu vermeiden, findet die Untersuchung in einem eigenen, abgeschirmten und störungsarmen Raum statt. Während der Messung sind Sie allein in diesem Raum (auf besonderen Wunsch kann auch ein Mitarbeiter mit im Raum sitzen). Sie werden allerdings

Appendix B(2): Information on EEG measurement

fortlaufend per Kamera und per Gegensprechanlage überwacht - das Personal befindet sich unmittelbar vor dem Raum.

Sie haben das Recht, jederzeit ohne Angabe von Gründen und ohne persönlichen Nachteil die Teilnahme an der Untersuchung abzulehnen oder während der Messung abzubrechen.

Risiken der EEG-Messung

Die EEG-Messung ist vollständig gefahrlos. Für das EEG werden nur solche Geräte verwendet, die den einschlägigen Sicherheitsbestimmungen genügen. Sie werden in gleicher Form auch für die klinische Routine eingesetzt.

Appendix C: Consent Form for EEG measurements

Einwilligungserklärung

Über die geplante elektroenzephalographische Untersuchung (EEG-Untersuchung) im Rahmen einer wissenschaftlichen Studie hat mich Frau / Herr ..... in einem Aufklärungsgespräch ausführlich informiert. Ich konnte alle mir wichtig erscheinenden Fragen, z.B. über spezielle Risiken und mögliche Komplikationen und über Neben- und Folgemaßnahmen stellen, die zur Vorbereitung oder während der Untersuchung erforderlich sind. Die mir erteilten Informationen habe ich inhaltlich verstanden. Mir ist bekannt, dass ich meine Einwilligung jederzeit ohne Angaben von Gründen widerrufen kann.

Ich weiß, dass die bei Untersuchungen mit mir gewonnenen Daten auf der Basis elektronischer Datenverarbeitung weiterverarbeitet und eventuell für wissenschaftliche Veröffentlichungen verwendet werden sollen. Ich bin mit der pseudonymisierten Verarbeitung dieser Daten einverstanden. Meine Daten werden nach Abschluss des Projekts bzw. spätestens nach zehn Jahren gelöscht. Auch diese Einwilligung kann ich jederzeit ohne Angabe von Gründen widerrufen.

Ich gebe hiermit meine Einwilligung, dass bei mir im Rahmen eines Forschungsvorhabens eine elektroenzephalographische Untersuchung meines Gehirns durchgeführt wird.

Ich erkläre mich damit einverstanden, dass meine persönlichen Daten in einer für die Öffentlichkeit nicht zugänglichen Datenbank erfasst werden. Die Speicherung meiner Daten dient ausschließlich der Möglichkeit einer erneuten Kontaktaufnahme des Instituts zum Zwecke der Vereinbarung weiterer Untersuchungen. Informationen zu meiner Person werden im Rahmen datenschutzrechtlicher Bedingungen verwaltet.

_____	_____	_____
Ort, Datum	Unterschrift Patient/Proband	Unterschrift Untersucher

Name .....

Adresse .....

Telefonnummer .....

Geburtsdatum ..... Alter .....

e-mail .....

Händigkeit ..... Geschlecht .....

Appendix D: Information on fMRI measurement

Informationsblatt für Probanden

Sehr geehrte Probandin, sehr geehrter Proband,

vielen Dank für Ihr Interesse an einer Studie, bei der die Aktivität im Gehirn während der Verarbeitung von Interferenzkontrolle untersucht werden soll. Wir möchten Sie zunächst über den Ablauf informieren, um Ihnen einen Überblick über die geplanten Messungen zu ermöglichen und Ihnen das Ziel der Untersuchung zu erklären.
Die Untersuchungen werden mit einem Magnetresonanztomographen (kurz MRT) durchgeführt, der uns Messungen der Durchblutung im Gehirn schmerzfrei und ohne zusätzliche Gabe von Medikamenten ermöglicht. Einige Personen werden die Untersuchung schon einmal erlebt haben, wenn hochauflösende Bilder vom Kopf im Rahmen der Diagnostik durchgeführt wurden.

Ziele der Untersuchung
Die Studie soll die Verarbeitung von Interferenzkonrolle in Abhängigkeit von verschiedenen kognitiven Alterungsprozessen untersuchen. Zu diesem Zweck werden Ihnen bei der Untersuchung wiederholt visuelle Reize gezeigt, die Sie entsprechend einer vorher vom Versuchsleiter erklärten Aufgabe bearbeiten sollen.

Was ist eine Magnetresonanztomographie?
Im Rahmen der Studie ist eine funktionelle Magnetresonanztomographie des Gehirns vorgesehen. Mit Hilfe dieser Methode ist es möglich, die Durchblutung in Ihrem Gehirn zu messen und daraus Rückschlüsse auf die bei der Aufgabe beteiligten Bereiche zu ziehen. Hierbei treffen Radiowellen, die in dem Magnetfeld erzeugt worden sind, auf den Körper, der Signale zurückschickt. Diese Echosignale werden von speziellen Antennen aufgefangen und in einem Computer ausgewertet.
Ein Kontrastmittel ist **n i c h t** erforderlich. Es werden **k e i n e** Röntgenstrahlen eingesetzt.

Wie läuft die Untersuchung ab?
Vor der Untersuchung werden Sie vom Untersuchungsleiter ausführlich über die für den Tag geplanten Messungen und Ziele informiert. Sie haben das Recht, ohne Angabe von Gründen die Teilnahme an der Messung abzulehnen. Auch im Verlauf der Untersuchung werden Sie vom Untersucher jederzeit gehört.
Für die Untersuchung müssen Sie sich auf eine Liege legen. Im Messbereich wird eine Kopfspule angebracht. Mit der Liege werden Sie dann langsam in die Röhre des Kernspintomographen geschoben. Dort befinden Sie sich während der gesamten Untersuchung, die ca. 60 Minuten dauert, in einem starken Magnetfeld, das für die Untersuchung benötigt wird.
Während der eigentlichen Messung sind sehr laute Klopfgeräusche zu hören, die völlig normal sind und von elektromagnetischen Schaltungen herrühren. Das Magnetfeld selbst können Sie weder spüren noch hören. Es ist von großer Bedeutung für die Qualität der Messungen, dass Sie während der Untersuchung möglichst ruhig liegen bleiben. Um dies zu erleichtern, werden Ihr Kopf und Arme mit Polstern und anderen Hilfsmitteln schmerzfrei gelagert. Die Aufgaben, die Sie während der Untersuchung zu bearbeiten haben, werden Ihnen über einen an der Kopfspule angebrachten Spiegel dargeboten.

Mögliche Risiken der Methode?
Der Kernspintomograph hält alle für die Sicherheit des Betriebes und insbesondere die Sicherheit der Probanden/Patienten erforderlichen Grenzwerte ein. Er wurde vom TÜV einer Sicherheitsprüfung unterzogen und wird darüber hinaus in den vorgeschriebenen Intervallen überprüft. Dennoch müssen folgende Punkte beachtet werden.

1. Auf ferromagnetische Gegenstände (z.B. Gegenstände, die Eisen oder Nickel enthalten) im Bereich des Magneten (z.B. Messer, Schraubenzieher, Kugelschreiber, Münzen, Haarspangen, ..) wird eine starke Anziehungskraft ausgeübt. Dadurch werden die Gegenstände mit großer Geschwindigkeit in den Magneten gezogen und können Personen erheblich verletzten.

2. Metallkörper und andere Fremdkörper wie Geschossteile können ebenfalls ferromagnetisch sein, durch magnetische Kräfte ihre Position im Körper verändern und dadurch innere Verletzungen hervorrufen.

3. Kleine Metallsplitter im Auge können durch magnetische Kräfte bewegt oder gedreht werden und das Auge verletzten.

4. Personen mit Chochlea-Implantaten, Defibrillatoren oder Pumpensystemen sollten nicht einem starken Magnetfeld ausgesetzt werden, da es auch in diesen Fällen zu Risiken durch magnetische Kräfte kommen kann.

5. Herzschrittmacher können im Magnetfeld ihre Funktionsfähigkeit verlieren. Deshalb dürfen Personen mit Herzschrittmachern nicht an Untersuchungen teilnehmen.

6. Bei der Messung mit dem Kernspintomographen kommt es zur Abstrahlung von hochfrequenter elektromagnetischer Strahlung, wie sie z.B. bei Radiosendern und Funktelefonen auftritt. Dies kann zu einer geringfügigen Erwärmung des untersuchten Gewebes führen.

7. Das Schalten der Magnetfeldgradienten führt in Teilen des Gradientensystems zu mechanischen Verformungen, die Geräusche mit Lautstärken über 100 dB erzeugen können. Deshalb müssen Sie bei allen Messungen entweder schallabsorbierende Kopfhörer oder Lärmschutzstopfen tragen, die von uns zur Verfügung gestellt werden. Bei Einhaltung dieser Vorsichtsmaßnahmen kann eine Schädigung des Hörsystems ausgeschlossen werden.

8. Manche Menschen erleben enge Räume als bedrohlich. Sie berichten über Unwohlsein z.B. in Fahrstühlen oder in großen Menschenansammlungen. Obwohl diese Angsterkrankung meist über die Anamnese ausgeschlossen werden kann, ist ein erstmaliges Auftreten während der Messung im Kernspintomographen möglich. Der Untersucher ist bei der Messung anwesend; bei dem Auftreten von Symptomen kann der Proband über Sprechkontakt bzw. über eine Notklingel jederzeit auf sich aufmerksam machen, so das eine rasche Intervention bei Symptomen gewährleistet ist.

Appendix E: Questionnaire with exclusion criteria for fMRI measurements

Fragebogen für Teilnehmer/innen an Kernspinresonanzuntersuchungen am Center for Advanced Imaging (CAI – Bremen)

Name:.....
Vorname:.....Geschlecht:.....
Geburtsdatum:.....
Straße/Hausnummer:.....
Wohnort:.....
Telefon:.....
Beruf:.....

Beantworten Sie bitte folgende Fragen zu möglichen Gegenanzeigen für Ihre Teilnahme an den Untersuchungen (Zutreffendes unterstreichen):

Sind Sie Träger eines Herzschrittmachers oder anderer elektrischer Geräte?	ja	weiß nicht	nein
Besitzen Sie metallische Implantate (z.B. Zahnschrauben oder metallische, mechanische Verhütungsmittel)?	ja	weiß nicht	nein
Befinden sich in Ihrem Körper andere metallische Fremdkörper?	ja	weiß nicht	nein
Wurde bei Ihnen eine Gefäßoperation durchgeführt?	ja	weiß nicht	nein
Haben Sie eine Allergie gegen Medikamente?	ja	weiß nicht	nein
Haben Sie Piercings oder Tätowierungen?	ja	weiß nicht	nein
Leiden Sie unter Platzangst?	ja	weiß nicht	nein
Sind bei Ihnen oder in Ihrer Familie Anfallsleiden (Epilepsie, Fallsucht) aufgetreten?	ja	weiß nicht	nein
Besteht die Möglichkeit, dass Sie schwanger sind?	ja	weiß nicht	nein

Beantworten Sie bitte folgende für unsere Untersuchungen wichtigen Fragen:

Sind Sie linkshändig oder rechtshändig?	Links	weiß nicht	rechts
Sind Sie Brillenträger/in?	ja	weiß nicht	nein
Tragen Sie Kontaktlinsen?	ja	weiß nicht	nein
Haben Sie Hörprobleme?	ja	weiß nicht	nein
Sind Sie mehrsprachig aufgewachsen?	ja	weiß nicht	nein

Ich habe alle Fragen auf dieser Seite wahrheitsgemäß und nach bestem Wissen beantwortet.

.....
Ort Datum Unterschrift der Probandin / des Probanden

Appendix F: Consent Form for fMRI measurements

Einwilligungserklärung

Über die geplante kernspintomographische Untersuchung (fMRT-Untersuchung) im Rahmen einer wissenschaftlichen Studie hat mich Frau / Herr ..... in einem Aufklärungsgespräch ausführlich informiert. Ich konnte alle mir wichtig erscheinenden Fragen, z.B. über spezielle Risiken und mögliche Komplikationen und über Neben- und Folgemaßnahmen stellen, die zur Vorbereitung oder während der Untersuchung erforderlich sind. Die mir erteilten Informationen habe ich inhaltlich verstanden. Mir ist bekannt, dass ich meine Einwilligung jederzeit ohne Angaben von Gründen widerrufen kann.

Ich weiß, dass die bei Untersuchungen mit mir gewonnenen Daten auf der Basis elektronischer Datenverarbeitung weiterverarbeitet und eventuell für wissenschaftliche Veröffentlichungen verwendet werden sollen. Ich bin mit der pseudonymisierten Verarbeitung dieser Daten einverstanden. Meine Daten werden nach Abschluss des Projekts bzw. spätestens nach zehn Jahren gelöscht. Auch diese Einwilligung kann ich jederzeit ohne Angabe von Gründen widerrufen.

Ich gebe hiermit meine Einwilligung, dass bei mir im Rahmen eines Forschungsvorhabens eine kernspintomographische Untersuchung meines Gehirns durchgeführt wird.

Mir ist bekannt, dass es sich bei der an mir vorzunehmenden kernspintomografischen Untersuchung um keine medizinische Untersuchung handelt und ich daher keine Rückschlüsse auf meinen gesundheitlichen Status ziehen kann. Im Falle eines Zufallsbefundes oder eines Verdachts auf einen Zufallsbefund möchte ich informiert werden.

Ich erkläre mich damit einverstanden, dass meine persönlichen Daten in einer für die Öffentlichkeit nicht zugänglichen Datenbank erfasst werden. Die Speicherung meiner Daten dient ausschließlich der Möglichkeit einer erneuten Kontaktaufnahme des Instituts zum Zwecke der Vereinbarung weiterer Untersuchungen. Informationen zu meiner Person werden im Rahmen datenschutzrechtlicher Bedingungen verwaltet.

_____	_____	_____
Ort, Datum	Unterschrift Patient/Proband	Unterschrift Untersucher

Name .....

Adresse .....

Telefonnummer .....

Geburtsdatum ..... Alter .....

e-mail .....

Händigkeit ..... Geschlecht .....

Decleration of Oath

Eidesstattliche Erklärung

(gemäß § 6 Abs. 5 der Promotionsordnung (Dr. rer. nat.) der Universität Bremen für die mathematischen, natur- und ingenieurwissenschaftlichen Fachbereiche)

Hiermit versichere ich, dass ich die vorliegende Arbeit mit dem Titel

Interference Control in Healthy and Pathological Ageing

selbstständig und ohne zulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus fremden Quellen direkt oder indirekt übernommenen Gedanken (wörtliche oder inhaltliche Zitate) sind als solche kenntlich gemacht.

Bremen, den

Ort, Abgabedatum Unterschrift des Verfassers