ROLE OF THE NEUROTRANSMITTERS DOPAMINE AND ACETYLCHOLINE DURING THE INTERACTION OF WORKING MEMORY AND ATTENTION

Dissertation

zur Erlangung des akademischen Grades

doctor rerum naturalium

(Dr. rer. nat.)

genehmigt durch die Fakultät für Naturwissenschaften

der Otto-von-Guericke-Universität Magdeburg

von Diplom-Biologin Anne-Katrin Vellage

geboren am 08.09.1984 in Berlin

Gutachter:

Prof. Dr. Notger G. Müller

Prof. Dr. Christiane Thiel

eingereicht am 24.06.2015

verteidigt am 16.09.2015

Kurzfassung

In unserer komplexen Welt sind wir permanent einer Fülle von sensorischen Reizen ausgesetzt. Um die für unsere Ziele relevanten Reize zwischen den irrelevanten Reizen selektieren zu können sind Mechanismen wie Aufmerksamkeit erforderlich. Da nicht alle relevanten Reize gleichzeitig verarbeitet werden können, ist ein Mechanismus nötig, sodass Informationen für einen kurzen Zeitraum aufrecht erhalten werden können, die nicht mehr auf unserer Retina verfügbar sind. Hierbei spielt das visuelle Arbeitsgedächtnis eine große Rolle, indem Informationen auch ohne visuelle Stimulation repräsentiert und diese Repräsentation moduliert werden kann. Die Menge an Information, die im Arbeitsgedächtnis gehalten werden kann, ist begrenzt und variiert interindividuell erheblich (Luck & Vogel, 1997). Studien legen nahe, dass Studienteilnehmer mit einer niedrigen Arbeitsgedächtniskapazität eine verminderte Fähigkeit haben, aufgabenirrelevante Informationen zu ignorieren. Stattdessen scheint es, als würden diese Studienteilnehmern unwichtige Informationen zusätzlich im Gedächtnis speichern (Vogel *et al.*, 2005; McNab & Klingberg, 2007). Die hier genannten Studien deuten auf eine Interaktion von selektiver Aufmerksamkeit und dem Arbeitsgedächtnis hin. Im Rahmen der vorliegenden Arbeit sollten der Zusammenhang zwischen Filter- und Speicherprozessen genauer untersucht werden. Dazu wurde ein „delayed match-to-sample"-Paradigma entwickelt indem sowohl die Merk- als auch die Aufmerksamkeitsanforderungen moduliert wurde. Da in vielen Studien mit steigender Merkanfoderung auch die visuelle Anforderung erhöht wurde und somit Gedächtnisprozesse nicht von visuellen Prozessen unterschieden werden konnten wurde das Paradigma in Hinblick auf dieses Problem angepasst, indem der visuelle Input unabhängig von der Modula-

tion bei allen Bedingungen gleich war. Zusätzlich wurde die Abfrage im Paradigma so entwickelt, dass die Unterscheidung von Antworten auf relevante und irrelevante Stimuli möglich war. Die vorher genannten Studien liefern keinen direkten Beweis, dass die irrelevante Information von den Studienteilnehmern mit geringer Arbeitsgedächtniskapazität tatsächlich ins Arbeitsgedächtnis aufgenommen wird, weil daraufhin gar nicht direkt getestet wurde. Ein Ziel der vorliegenden Arbeit war es daher mittels des angepassten Paradigmas den direkten Nachweis zu erbringen, dass das Speichern von unnötiger Information zu einer erhöhten Fehlerrate und längeren Reaktionszeiten bei Studienteilnehmer mit niedriger Arbeitsgedächtniskapazität führt. Des Weiteren sollten die neuronalen Korrelate von Gedächtnis- und Aufmerksamkeitsprozessen untersucht werden. Dazu wurde das Paradigma im Kernspintomographen durchgeführt. Studienteilnehmer waren gesunde junge und ältere Menschen, um auch Veränderungen der genannten Prozesse im Alter zu untersuchen. Zusätzlich zu dem beschriebenen Paradigma nahm jeder Studienteilnehmer an einem Arbeitsgedächtnistest teil, sodass an Hand der Leistung in diesem Test die individuelle Gedächtniskapazität errechnet werden konnte.

Sowohl eine Erhöhung der Aufmerksamkeitslast als auch eine Erhöhung der Merklast führten zu vermehrten Fehlern bei den Studienteilnehmern. Defizite bei älteren Teilnehmern waren auf die Bedingungen in denen selektives Filtern von Information erforderlich war beschränkt, ein tendenzielles Defizit war aber auch beim reinen Merken von Informationen zu sehen. Als neuronales Korrelat von Speicherprozessen konnte unter anderem der inferiore Parietalkortex in beiden Altersgruppen identifiziert werden. Die hämodynamische Antwort in dieser Hirnregion war außerdem mit den Antworten auf die Abfrage der irrelevanten Stimuli assoziiert. Die Präsentation von Distraktoren neben den Zielreizen führte zu stärkerer Suppression von parietaler Aktivität, und damit auch bei manchen Studienteilnehmern in Abhängigkeit davon zu weniger Fehlern und schnelleren Antworten. Der inferiore Parietalkortex scheint somit eine Hirnregion zu sein, die die Interaktion zwischen Gedächtnis und Aufmerksamkeit

kontrolliert. Die neuronalen Antworten im Parietalkortex waren dabei unabhängig von der individuellen Arbeitsgedächtniskapazität.

Des Weiteren konnten zahlreiche Hirnregionen identifiziert werden, die bei dem Filtern von Informationen eine Rolle spielen. In beiden Altersgruppen waren der bilaterale Thalamus, bilaterale Basalganglien, rechter mediale Frontalkortex, Occipitalkortex und superiore Parietalkortex in die Informationsselektion involviert.

Kognitive Mechanismen wie Aufmerksamkeits- und Arbeitsgedächtnisprozesse sind wesentlich an das funktionierende Zusammenspiel von Neurotransmittern im Gehirn gebunden. Den beiden Neurotransmittern Acetylcholin und Dopamin kommt auch bei zwei wichtigen neurodegenerativen Erkrankungen, der Alzheimer-Demenz (AD) und der Parkinsonerkrankung (PD), entscheidende Bedeutung zu. AD Patienten leiden auf Grund einer Degeneration des Nucleus basalis Meynert an einem vorwiegend cholinergen, PD Patienten dagegen aufgrund der Degeneration der Substantia nigra an einem dopaminergen Defizit. Die genauen Zusammenhänge zwischen Dopamin bzw. Acetylcholin und Speicher- bzw- Filterprozessen sind jedoch unklar. Ein weiteres Ziel der vorliegenden Arbeit war es deshalb zu untersuchen, wie die selektive Aufmerksamkeit und die Speicherung von Informationen in das Arbeitsgedächtnis durch pharmakologische Modulation von Neurotransmitterspiegeln im Gehirn beeinflusst werden. Zu diesem Zweck wurden den Studienteilnehmern vor den Messungen Medikamente verabreicht (Galantamin, Levodopa), die die Neurotransmitterkonzentration von Dopamin und Acetylcholin im Gehirn selektiv erhöhen sollten. Weiterhin sollte untersucht werden, inwiefern Polymorphismen der für das cholinerge bzw. dopaminerge System codierenden Gene (DBH, COMT, CHRNA4) und die strukturelle Integrität des cholinergen basalen Vorderhirns bzw. des dopaminergen Mittelhirns die individuellen visuellen Selektions- bzw. Gedächtnisleistung beeinflussen.

Die Ergebnisse legen nahe, dass der postulierte Zusammenhang zwischen Dopamin und dem Arbeitsgedächtnis auf der einen Seite und Acetylcholin und selektiver Aufmerksamkeit auf der anderen Seite zu vereinfacht ist. Erhöhung des Dopaminspiegels führte zu einer schlechteren Leistung in der Gedächtnisaufgabe in Abhängigkeit von der

individuellen strukturellen Ausstattung. Diese Verschlechterung ist vermutlich auf einen nicht optimalen Dopaminspiegel zurückzuführen, der zu Beeinträchtigungen von kognitiven Leistungen führen kann. Des Weiteren wurden Zusammenhänge zwischen Dopamin und filterrelevanten Hirnregionen gefunden. Auch die Gabe des Acetylcholinesterasehemmers Galantamin hatte sowohl einen Einfluss auf das Filtern von Informationen als auch das Speichern von Informationen. Auch in Hinblick auf den genetischen Hintergrund der Studienteilnehmer zeigten Veränderungen in Dopamin und Acetylcholin modulierenden Genen sowohl deutliche Effekte auf die Leistung, als auch in strukturellen und neuronalen Korrelaten von Speicher- und Filterprozessen.
Die Ergebnisse der vorliegenden Arbeit weisen auf einen deutlichen Zusammenhang zwischen Arbeitsgedächtnis- und Aufmerksamkeitsprozessen hin. Der inferiore Parietalkortex scheint dabei ein wichtiger Knotenpunkt bei der Aufmerksamkeitskontrolle und Verarbeitung von relevanten sowie irrelevanten Informationen zu sein. Durch pharmakologische Neurotransmittermodulation konnte gezeigt werden dass die erfolgreiche Interaktion der genannten Prozesse stark von dem Zusammenspiel von Dopamin und Acetylcholin abhängig ist. Ein besseres Verständnis von Aufmerksamkeits- und Arbeitsgedächtnisprozessen und zugrunde liegenden neurobiologischen Mechanismen trägt zu einem besseren Verständnis von Erkrankungen wie Alzheimer-Demenz und Parkinson bei und ist bei der Entwicklung von therapeutischen Strategien unerlässlich.

Abstract

The filtering of irrelevant and the storage of relevant information constitute two crucial processes of human visual working memory. However, it is unclear which brain networks sustain these processes and how they are modulated by neurotransmitters like acetylcholine and dopamine. In order to answer these questions, a combined working memory and attention paradigm was developed that controlled for perceptual load such that all conditions involved the same number of stimuli. Storage and filtering were assessed in trials that consisted of high and low demand on both of these processes. In addition, lure trials were included (probes presented in locations previously occupied by distractors) to directly assess whether irrelevant information was also encoded. After administration of an acetylcholine or dopamine-modulating drug, healthy young and elderly participants completed the working memory and attention task whilst they underwent functional magnetic resonance imaging (fMRI) scanning. In addition, genetic and structural factors were identified that are involved in the dopaminergic and cholinergic system.

The inferior parietal cortex was identified as a neural substrate for the interaction of memory and filtering because memory-related hemodynamic response in this brain region correlated with performance in lure trials in both age groups. The assumption that reduced or suppressed parietal activity induced by the additional representation of distractors reflects unnecessary storage of these items has not been demonstrated directly before. Furthermore, the cholinergic gene polymorphism CHRNA4 was associated with this parietal memory-related activity. In addition to memory related brain regions, a large network of co-activated regions was found during filtering that overlapped in cortical and subcortical regions across both age cohorts. Alongside the involvement in memory processes, dopamine was found to be involved in filter processes via a subcortical gatekeeper network. In addition, compensatory mechanisms were observed in elderly participants with a broader and bilateral recruitment of brain

regions during memory and filter processes in comparison to young, reflecting the use of different performance strategies to cope with the task demands.
The present results provide strong evidence for the interaction between visual working memory and filtering processes. The degree of interaction and effects on performance might thereby be dependent on the neurotransmitters dopamine and acetylcholine, as well as on age related changes in structural, functional and genetic factors.

Contents

List of Figures

List of Tables

Abbreviations

AD	Alzheimer's disease
ANOVA	Analysis of variance
BOLD	Blood oxygen level dependent
CDA	Contralateral delay activity
CHRNA4	Choline receptor subunit alpha-4
COMT	Catechol-o-methyl-transferase
DBH	Dopamine-beta-hydroxylase
EEG	Electroencephalography
FDR	False discovery rate
FEF	Frontal eye field
FFA	Fusiform face area
fMRI	Functional magnetic resonance tomography
Hb	Hemoglobin
IFG	Inferior frontal gyrus
IPS	Inferior parietal sulcus
MFG	Middle frontal gyrus

MMST Mini mental status test

MNI Monteral neurological institute

MT Magnetization transfer

OCC Occipital cortex

OSPAN Operation word span task

PC Parietal cortex

PD Parkinson's disease

PET Positron emission tomography

PFC Prefrontal cortex

PHC Parahippocampal cortex

PPA Parahippocampal place area

RNA Ribonucleic acid

ROI Region of interest

SEM Standard error of the mean

SMA Supplementary motor area

TC Temporal cortex

TMS transcranial magnetic stimulation

VWM Visual working memory

1 Introduction

Surviving in a complex world in which our senses are stimulated permanently necessitates mechanisms like attention, that help us to focus on our goals without being distracted. An essential component of attention is the selection of information that is relevant to our task at hand. When relevant and irrelevant stimuli compete with each other for further processing, they have to be held "on line" for a small amount of time to select the ones that are relevant for the current goal. Visual working memory (VWM) fulfills this role by maintaining information for a short time that is no longer represented on our retina. The interaction between VWM and selective attention and the underlying neural mechanisms are the main topics of the present dissertation. The concepts of both processes and the current status of research will be discussed in the following sections. In addition, a special focus will be made on the role of the neurotransmitters dopamine and acetylcholine during these processes. Furthermore, recent literature on the effects of memory and attention processes with regard to healthy aging will be reviewed.

1.1 Concept of selective attention

In general, attention can be focused onto a certain aspect of a visual scene or be divided between several aspects. A shift of the attentional focus onto a certain aspect of a visual scene can be associated with the movement of the eyes to the aspect of interest (overt attention). In the 19th century Helmholtz provided evidence for the realignment of attention without any movement of the eyes or body (covert attention). In the study

of Helmholtz (1867) participants were asked to fixate a certain point in the middle of a board full of letters while sitting in a darkened room. The room was then illuminated for a short time by means of a flash. Without moving their eyes to a certain location, participants were able to name the letters presented in a location they were previously attending to. Based on this study the spotlight model of attention was established and further developed (Posner, 1980). In the following years, it was shown that the radius of the mental spotlight can vary based on environmental requirements (zoom lens model) but that an increase in the size of the attentional spotlight is associated with a decrease in precision of the current representation (Eriksen & James, 1986). In support to these theories significantly different neural changes were found, when a stimulus was presented in an attended location in contrast to an unattended location (Hillyard & Mangun, 1987). A widely accepted model describing the characteristics of spatial attention is the Mexican hat model (Pan & Eriksen, 1993; Cave & Bichot, 1999; Müller *et al.*, 2005). Following this model, the visual representation in the spotlight of attention is enhanced in the middle and to a lower extent in the periphery of the spotlight but inhibited around the center of the focus. The model was later supported by neural and behavioral findings in humans and macaques (Wegener *et al.*, 2004, 2006; Hopf *et al.*, 2006).

Alongside spatial based attention, attention can also be directed to certain features independent of the spatial focus of attention in a visual scene. With single cell recordings in monkeys it was shown that neurons sensitive for color or motion for instance, respond to the presentation of a preferred color or motion in the whole receptive field (Motter, 1994; Treue & Trujillo, 1999). The reported results were replicated in humans as well by means of non-invasive techniques like functional magnetic resonance imaging (fMRI), allowing the indirect estimation of neural activity (Saenz *et al.*, 2002, 2003). The measured signal in the studies of Saenz and colleagues was enhanced in brain areas sensitive to motion when a moving stimulus in the non-attended field had the same direction as the goal relevant moving stimulus in the attended field. Hence, in contrast to location based attention, feature based attention seems to work on a

global level. Moreover, if a feature of a certain object had to be attended, it was found that other features of the same object were processed as well, although the additional processing was not required for the task at hand (O'Craven *et al.*, 1999). Consequentially, attention is deployed to a whole object instead of to a single feature of an object only. This process is referred to as object based attention.

Defined by internal goals and cognitive factors like expectation and knowledge, selective attention can be deployed endogenously to certain locations, features or objects (top down). In contrast, selective attention can be driven by external stimuli (bottom up) that automatically capture attention, e.g. because of certain characteristics. It seems that we are biased towards salient stimuli in the absence of goal relevant, top down driven factors. This view is supported by a study of Mathôt and colleagues (2010) in which a distractor was presented simultaneously, shortly after or shortly before the target onset either in the same or opposite visual field. Interference in terms of higher reaction times was strongest, when the distractor was presented with or shortly after the target onset in the same visual field. Interestingly, interference was also strong when the distractor was presented in the opposite visual field before target onset. The authors concluded that the salient distractor captured attention before the goal relevant target had appeared and that a switch of attention to the target location in the opposite visual field resulted in higher reaction times. The interference effects during presentation of distractor and target in the same visual field can be explained by the biased competition model (Desimone & Duncan, 1995). We are not able to process all visual information that is presented on our retina, at a certain point visual objects compete with each other. In this case we are predisposed towards information that is needed to achieve our goals, so that stimuli in the focus of attention compete with each other whilst unattended stimuli do not, like shown in the study of Mahôt and colleagues (2010).

New methods like fMRI, electroencephalography (EEG), transcranial magnetic stimulation (TMS) and transcranial alternating or direct current stimulation have been developed in the last decades to investigate underlying brain mechanisms with the

advantage of being mainly non-invasive. Insights from these methods with regard to selective attention will be reported in the following section.

1.1.1 Neural correlates of selective attention

Early studies investigating attention with the technique of fMRI revealed increased activity in striate and extrastriate visual cortices when corresponding stimuli were attended to (Heinze *et al.*, 1994; Brefczynski & DeYoe, 1999; Gandhi *et al.*, 1999; Martinez *et al.*, 1999; Somers *et al.*, 1999; Kastner & Ungerleider, 2001), supporting the ideas of the biased competition model (Desimone & Duncan, 1995). Later it was assumed, that this activation enhancement might be the result of attentional control processes that lead to enhanced activity in visual cortices via feedback connections in favor of the relevant targets for the task at hand, rather than effects of visual input per se (Martinez *et al.*, 1999; Hopfinger *et al.*, 2000a; Noesselt *et al.*, 2002). An eligible candidate for the control of attentional processes is the prefrontal cortex (PFC) with its feed forward and feedback connections to most of the extrastriate visual cortices (Swick & Knight, 1998; Miller & D'Esposito, 2005). In the last decade, this claim was substantiated by several researchers supporting the putative role of PFC as a control region (Corbetta & Shulman, 2002; Pessoa *et al.*, 2003; Pessoa & Ungerleider, 2004; Postle, 2005; Lepsien & Nobre, 2006; Burgess *et al.*, 2007a,b).

Because a neural system that accounts for the different aspects of selective attention (top down vs. bottom up) has to be highly dynamic, two segregated networks including PFC were assumed to be responsible for these two processes (Corbetta & Shulman, 2002). To study top down and bottom up processes, a certain kind of task classically referred to as the Posner paradigm is frequently used (Posner, 1980): A cue (e.g. arrow) is directing attention to a certain feature (e.g. location). The cue can be endogenous by directing attention to another location than the cue is presented. In contrast, a cue is called exogenous when the target is presented on the exact location that was cued before. A target is presented after the cue that can be either at the cued location (valid) or at an uncued location (invalid). Invalid trials require a re-

orientation of attention and refer to bottom up processes whereas valid trials refer to top down processes. Corbetta and Shulman (2002) reviewed several papers in which attentional processes were studied with similar paradigms using fMRI and which reported segregated frontoparietal networks for top down and bottom up processes. A dorsal frontoparietal network was postulated to be involved in the top down control of visual attention. The network consists of a posterior part, namely the dorsal parietal cortex (PC) with parts in the superior parietal lobes and the intraparietal sulcus (IPS) and an anterior part with the dorsal frontal cortex along the precentral sulcus, close to the frontal eye field (FEF). Following Corbetta's review (Corbetta & Shulman, 2002; Corbetta *et al.*, 2008), a ventral frontoparietal network controls bottom up processes. Pivotal regions of the ventral network are the area where occipital, parietal and temporal lobes meet, also known as temporo parietal junction, as well as frontal regions including inferior frontal gyrus (IFG), anterior insula, frontal operculum and middle frontal gyrus (MFG). In addition, the IPS and FEF are also activated in the ventral network. Furthermore, ventral and dorsal frontoparietal networks seem to be more dominant in the right hemisphere (Shulman *et al.*, 2002). The question of how both networks interact and whether some parts of each network implement different tasks is still of great interest for researchers and not yet answered. It seems that the ventral network interrupts the dorsal network when reorientation of attention is demanded. Conversely if top down processes are accomplished, activation of regions in the ventral network are suppressed or brain regions are just not recruited to prevent distraction (Shulman *et al.*, 2003; Todd *et al.*, 2005; Kincade *et al.*, 2005; Wen *et al.*, 2012). In terms of specialization Corbetta and colleagues propose a stimulus specific selection mechanism in the PC based on the findings of differential parietal activations for motion (Shulman *et al.*, 2002), location (Yantis *et al.*, 2002), and other stimuli features (Le *et al.*, 1998; Wojciulik & Kanwisher, 1999) but its exact role remains unclear.
Besides these cortical networks, subcortical structures like the basal ganglia and the thalami are assumed to form a basis for attentional control together with the PFC (Frank *et al.*, 2001; Haber & Mcfarland, 2001; LaBerge, 2002; Hazy *et al.*, 2007). The

thalami are seen as a relay station or primary filter that integrates sensory input (e.g. from the retina) and forwards this information to the corresponding cortices (e.g. visual cortex, Guillery & Sherman, 2002). Soto and colleagues (2007) observed enhanced connections between the thalamus and PFC in a Posner paradigm during valid trials in comparison to invalid trials, suggesting an important role of the thalamus during top down processes. Because the thalami are receiving input from cortical structures, it is likely that it does not act as an autonomic control structure during attentional processes. In addition, the thalami are also modulated by the basal ganglia via "cortico-basal ganglia-thalamocortical" loops (Alexander *et al.*, 1986; McHaffie *et al.*, 2005). However, the exact interplay between those structures remains unclear. In a study of McNab and Klingberg (2007) the basal ganglia were identified as being involved in the preparation of filtering out goal relevant information that was later stored in VWM, suggesting an pivotal role as a transfer station between attention and VWM.

1.2 Concept of visual working memory

Whereas in the last century a more storage oriented role was attributed to VWM (Miller *et al.*, 1960; Atkinson & Shiffrin, 1968), today VWM is referred to as a more processing oriented system that maintains and modulates information (Baddeley & Hitch, 1974; Baddeley, 2000). The most accepted model is the three component model of VWM from Baddeley and Hitch (1974) which describes a supervisory central executive as control component with limited capacity and two slave systems: a phonological loop for verbal information and a visual-spatial sketch pad. Whereas language as well as the sound of language is processed in an articulatory loop and an acoustic store of the phonological loop, visuo-spatial information is assumed to be mainly processed in a visuo-spatial sketchpad. The model was further advanced to account for the interaction between VWM and long term memory by including the episodic buffer (Baddeley, 2000).

1.2.1 Neural correlates of visual working memory

Investigating the neural correlates of working memory, a growing body of literature has arisen in the past decades. Following Baddeley's model of working memory assuming a central executive, the PFC has come in the focus of research. Early hints for a substantial involvement of PFC in working memory processes came from lesion studies in monkeys (Miller & Orbach, 1972; Bauer & Fuster, 1976; Funahashi *et al.*, 1993). In addition, single cell studies revealed sustained activity in prefrontal neurons even after a visual stimulation was absent (Fuster & Alexander, 1971; Chafee & Goldman-Rakic, 1998). Similar to attention research, research on working memory was markedly influenced by the finding that the brain seems to be segregated into dorsal and ventral pathways (Ungerleider & Mishkin, 1982; Mishkin *et al.*, 1983). Goldman-Rakic (1987) claimed that this functional segregation in PFC results in a dorsal part that is involved in the storage of spatial information whereas the ventral part is engaged in the storage of object information. Aside from the PFC sustained responses to stimuli were also found in the PC and temporal cortex (TC) after withdrawal of visual stimuli (Chafee & Goldman-Rakic, 1998; Miller & Desimone, 1994), which seems to support the idea of functional segregated pathways for object and location based memory. Indeed neural responses to memory of spatial information were found in PC, whereas selective neural activation to memory of objects was found in ventral regions like inferior TC and IFG (Ranganath *et al.*, 2004; Rottschy *et al.*, 2012). The essential role of the PC in memory was further confirmed in studies reporting VWM deficits in patients with PC lesions (e.g. Baldo & Dronkers, 2006; Finke *et al.*, 2006).

A difficulty in investigating the neural correlates of VWM is the variety of different tasks that are used. VWM is usually tested with the n-back task, delayed matching-to-sample paradigm or the Sternberg task. The latter is a test developed by Saul Sternberg (1963; 1966) and comprises a list of stimuli (words, letters, objects etc.). After a short delay, participants have to report whether a certain stimuli was part of the list or not. The classical n-back task (Kirchner, 1958) consists of a stimuli list as well. Participants have to follow this list and report whenever a stimulus is repeated

directly (1-back), with one other stimulus in between (2-back) and so on. In a delayed matching-to-sample task a set of stimuli is presented and repeated after a delay. The repeated set can either be exact the same as the former or one or more of the targets can have changed identity or location and participants are asked to report a change (change detection).

Rottschy and colleagues (2012) made an attempt to find a "core" network of VWM that is engaged across the different VWM tasks and across all phases of VWM (encoding, maintenance, retrieval) by conducting a meta-analysis over 189 experiments. The authors identified bilateral activations in posterior MFG, IPS, insula, pars opercularis of the IFG and lateral PFC being involved in VWM processes independent of task. Further insights into a specialization of brain regions for certain VWM processes are coming from studies using methods consisting of varying memory loads. Increasing the memory load of a certain type of stimuli increases activation in PC and occipital cortex (OCC, Todd & Marois, 2004, 2005; Xu & Chun, 2005). The fact that the PFC is not load sensitive might stem from its control function whereas the PC might act as a storage region per se. Several studies not only identified the PC as a storage region but also revealed it as the possible determinant for VWM capacity (Todd & Marois, 2004, 2005; Vogel & Machizawa, 2004; Vogel *et al.*, 2005; Xu & Chun, 2005; McNab & Klingberg, 2007). Xu and Chun (2005) presented a set of stimuli with a varying set size of one to eight stimuli in a delayed matching-to-sample task. After a short retention interval one of the prior presented stimuli was probed and participants had to respond by button press if the stimulus was part of the former set. FMRI activation in bilateral PC increased with increasing set size but reached a plateau with a set size of three to four items confirming the VWM capacity limit of behavioral studies (Miller, 1956; Luck & Vogel, 1997; Zhang & Luck, 2008; Cowan, 2004). Because participants had to memorize object location and identity in the previously described study, the authors emphasized the memory independent role of the PC in the integration of different features (Friedman-Hill SR, 1995; Shafritz *et al.*, 2002), but the exact role of PC in VWM processes remains still unclear. Especially when distractors enter the equation,

it is doubtful whether this irrelevant information is filtered out on the perceptual level or whether that information is stored somewhere competing with the relevant information.

1.3 Interaction between visual working memory and selective attention

The fact, that information has to be temporally maintained to select relevant amongst irrelevant information is not the only hint that VWM and selective attention might be intertwined. A strong support for the interaction between both mechanisms comes from several studies showing that both are limited or depend on the same limited resources respectively (Sperling, 1960; Pashler, 1988; Pylyshyn & Storm, 1988; Irwin & Gordon, 1998; Sears & Pylyshyn, 2000; Vogel *et al.*, 2001; Scholl, 2001; Culham *et al.*, 2001; Alvarez & Cavanagh, 2004; Oksama & Hyönä, 2004; Cavanagh & Alvarez, 2005; Fougnie & Marois, 2006). In these studies usually the VWM or attentional load is increased beyond the limit which is reflected in behavioral parameters (e. g. Pylyshyn & Storm, 1988; Luck & Vogel, 1997; Scholl, 2001; Alvarez & Cavanagh, 2004; Todd & Marois, 2004; Xu & Chun, 2005).

1.3.1 Constraints of selective attention:

Similar to VWM, attention seems to be limited to three to five objects that can be attended simultaneously (Pylyshyn & Storm, 1988; Scholl, 2001; Alvarez & Cavanagh, 2004). In a study of Alvarez and Cavanagh (2004) participants were tested with a change detection paradigm investigating VWM and a visual search paradigm to study selective attention. In the first part a number of stimuli varying from one to fifteen from a certain category (shaded cubes, random polygons, Chinese characters, letters and colored squares) was presented for a short time (Fig. 1.1). After an interval with a blank screen, either the same or a similar display was presented with one stimulus

having changed identity. Participants were then asked to report whether they had detected a change. In the second part of the study a target was presented, followed by a blank interval. Afterwards, an array with a number of four, eight or twelve objects from the target class was presented, containing the target in half of the trials. Again participants had to report if the target was present. As an index for VWM capacity the number of objects was estimated for each stimulus class in which participants reached 75 % correct. An index for good visual search performance (search rate) was calculated by dividing reaction times from trials in which the array contained the target by the presented set size. Correlating search rate and object threshold a highly significant relationship between both measures was found ($r^2 = .992$). Interestingly, the limit of more complex objects like shaded cubes was smaller than the limit for simple objects like letters or colored squares during both tasks supporting a limit defined by information load rather than concrete object numbers.

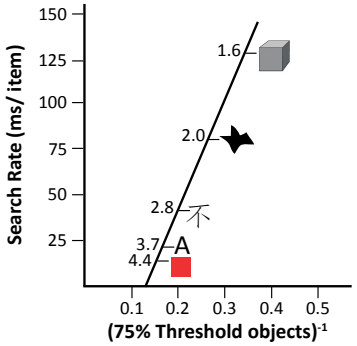

Figure 1.1: Correlation between search rate and memory performance (modified from Alvarez & Cavanagh, 2004)

1.3.2 Constraints of visual working memory

A landmark in studying the limits of VWM was a study by George Sperling who presented an array of twelve letters to participants (Sperling, 1960). After the letters had disappeared participants had to report as many letters as possible leading to an average of four to five items that were rehearsed accurately. Luck and Vogel investigated VWM in terms of certain features and showed a capacity limit of four items for colors or orientations respectively (Luck & Vogel, 1997). Because participants were even able to remember both, the color and orientation of four items, the authors concluded, that VWM is rather processing integrated objects instead of single features. Until today researchers are divided on the exact contents that is leading to the limit of VWM (Brady *et al.*, 2011). Meanwhile some researchers support the idea of a concrete item limit in VWM (Miller, 1956; Luck & Vogel, 1997; Cowan, 2004; Zhang

& Luck, 2008) others advocate the theory of a limit that is determined by the amount of information (Alvarez & Cavanagh, 2004; Wilken & Ma, 2004; Bays & Husain, 2008). To compare limits across different visual memory paradigms an attempt to develop a standardized measure for individual VWM capacity (K) was made by Pashler (1988) and Cowan (2001):

a) Pashler, 1988:

$$K = S(\frac{H - F}{1 - F}) \tag{1}$$

b) Cowan, 2001:

$$K = S(H - F) \tag{2}$$

In these formulas S is the number of items that have to be remembered and H and F are the observed hit and false alarm rates. Both measures take a probability of guessing into account. The formula of Pashler was based on a paradigm in which a set of stimuli was presented again after a short delay with one of the stimuli having changed in 50 % of the trials. This type of paradigm is classically described as a chance detection paradigm (Phillips, 1974) in which the whole display is probed. In contrast, the formula of Cowan - to index VWM capacity - was evaluated for a change detection paradigm in which a single item is probed. Having an amount of items in memory, the probability of responding correctly is different, depending on the number of probed items. Both measures account for the probability in the respective paradigms and should be used carefully depending on the item size of the probed display (Rouder *et al.*, 2011). Furthermore, with regard to the fact that both measures presume a discrete slot model of VWM, results have to be interpreted carefully.

In most of the previously mentioned theories VWM and selective attention are treated as separate constructs which is not a universally accepted concept. For example, Cowan and colleagues see VWM as a temporarily activated part embedded in long term memory (Cowan, 1988, 1995, 2004). Parts of this activated representations can then be highlighted by attention whence it follows that the attention limit defines the memory limit. A further theory about the interplay of selective attention and VWM

comes from Kiyonaga and Egner (2013), who see VWM more or less as an attentional construct. Whether attention is directed towards external perceptual information (selective attention) or towards internal representations, depends on a supervisory construct whose resources are limited. The idea of working memory as an attentional component is in line with Baddeley (1993), who suggested the term "working attention" instead of working memory because of the strong link between these mechanisms.

1.3.3 Shared neural correlates

With regard to the modulating role of a frontoparietal network in attention, it seems that an identical network is involved in VWM processes. Discussing memory processes in the face of distraction and considering the limitation of the VWM system, filter mechanisms become necessary that select goal relevant amongst irrelevant information. It seems that filtering of distractors is highly dependent on top down modulation of visual areas, explaining the similarity of brain structures involved in VWM and attentional control processes.

The rather modulating role of the PFC in a VWM task including distractors, was confirmed by a study of Feredoes and colleagues (Feredoes *et al.*, 2011) utilizing the method of combined TMS-fMRI. Participants had to memorize three faces or houses and either distractors of the opposite category (houses for target faces and vice versa) were absent or present in the delay period. Applying TMS over the dorsolateral PFC during the delay period modulated activity only during the presence of distractors. Furthermore, this modulation was restricted to visual areas processing the memorized targets (parahippocampal place area (PPA), fusiform face area (FFA)) not the distractors, suggesting a protecting role of the dorsolateral PFC that only becomes necessary during distraction. In a study of Mayer and colleagues (2007) a visual search task was combined with a delayed matching-to-sample task to investigate shared neural correlates of selective attention and VWM. Alongside the task modulation, the memory and search load was modulated while the visual input was kept constant. FMRI results revealed common neural activations in posterior and frontal regions as well as

in visual cortex, insula and premotor cortex. Increasing VWM load and difficulty of visual search was leading to increased neural activity in the right PFC and bilateral insulae. Ambiguous results were found for visual, parietal and premotor areas. Activation in these regions increased with increasing VWM load as well, but this increase was reduced during the attentional demanding search condition compared to the easy search condition. The authors linked these results to the concept of shared limited resources. If a certain limit is reached, in this case by an attentional high demanding task, no resources are spared for the VWM. Vogel and Machizawa (2004) introduced an electrophysiological measure, the contralateral delay activity (CDA) that is sensitive to memory load. The CDA appears at the posterior part of the scalp contralateral to the side containing the memorized stimuli and is increasing with increasing memory load. Similar to blood oxygen level dependent (BOLD) activation in the study of Xu and Chun (2005) the CDA amplitude peaks when a set size of three to four is reached but the exact limit varies between individuals. To find out the exact number of items that was memorized the authors calculated the VWM capacity with the formula of Cowan (formula 2, p. 11). The resulting individual capacity correlated significantly with the amplitude difference between two and four items showing a direct reflection of individual VWM capacity limit in posterior neural activity. Based on these results, Vogel and colleagues showed in a second study (Vogel *et al.*, 2005) that the individual VWM capacity reflected in CDA differences is dependent on efficient filtering of distractors.

The previous discussed studies support the idea of shared limited resources for VWM and selective attention. It seems that a frontoparietal network asserts control over visual areas, processing a certain stimulus type of the task at hand. This modulation becomes important under distraction. In an fMRI study of McNab and Klingberg (2007) the interplay between those brain areas during the selection and maintenance of relevant targets among distractors becomes clearer. Participants were tested in a delayed matching-to-sample task containing varying memory load under presence or absence of distractors. Whether a distractor was presented or not was indicated by a

symbolic cue at the beginning of each trial. When the presence of distractors was cued, neural activation was highest in MFG and left basal ganglia. The authors defined this activation pattern as "filtering set activation" that recruits the resources needed to prevent the processing of relevant targets from distraction. Furthermore, the authors found the right PC being sensitive to memory load consistent with other studies (Xu & Chun, 2005; Todd & Marois, 2004, 2005). Parietal activation during the encoding of targets presented alongside with distractors was depended on the individual filtering set activity in the basal ganglia. Participants with a low filtering set activity in expectation of a distractor showed higher parietal activity during the distractor condition, assuming an unnecessary storage of irrelevant information. Higher filtering set activity and apparently better top down control prevented distractors from entering the parietal memory store leading to lower parietal activity. In addition to these results, the individual VWM capacity was positively correlated with the filtering set. This result is a further hint that the limit up to which top down control can be sufficiently performed is constrained by the VWM limit, leading to the conclusion of shared finite resources.

1.3.4 Which process asserts control over which?

The previously mentioned studies support the idea, that working memory and selective attention are linked but the kind of interaction remains unclear. Many researchers agree on attention being the critical mechanism that controls which information is stored in memory (e.g. Broadbent, 1957; Engle *et al.*, 1999; Kane *et al.*, 2001) but conversely some researchers attribute a more active and guiding role to VWM (e.g. Desimone & Duncan, 1995; Kiyonaga & Egner, 2013).

Impact of Selective Attention on Visual Working Memory One of the early theories supporting the role of selective attention as a control mechanism was the filtering theory from Broadbent (Broadbent, 1957; Broadbent Donald, 1958). Following Broadbent's filtering model, all sensory information enters an unlimited sensory buffer in

a first step and passes a single channel that acts like a bottleneck in a second step. This channel is defined by current goals and is only passable for relevant information. After these steps information is further processed, e.g. by VWM. Because - following Broadbent's filtering model - only relevant information is able to pass the channel, the model cannot explain interference by distractors. Treisman (1960) came up with a revised model assuming that irrelevant information that is in the sensory buffer is rather attenuated than completely filtered out making interference on higher processing levels possible. The previous described filtering theories are in line with those of other researchers who support the idea of an early selection of information (Cherry, 1953; Neisser, 1969) but were challenged by the idea of a late selection of information (Deutsch & Deutsch, 1963; Duncan, 1980; LaBerge, 1975; Allport, 1977). Late selection theories propose, that all sensory information has to be analyzed and therefore maintained for a short time before relevant information can be chosen. Combining both approaches and attributing a more dynamic role to attention, the perceptual load theory was developed by Lavie and colleagues (Lavie & Tsal, 1994; Lavie, 1995; Lavie & De Fockert, 2005). According to the perceptual load theory perception is limited. In case of high load of relevant information, the perceptual limit is reached and irrelevant information is not processed. However, if load of relevant information is low, spare resources will spread to irrelevant information leading to distraction and attentional selection is carried out late. Early selection only takes place under high perceptual load, which can be either achieved by a greater amount of items or by more complex items (Lavie & De Fockert, 2005). Another explanation for low interference effects under high perceptual load comes from the dilution theory (De Fockert, 2013). Following this theory, irrelevant information is perceived also under high load, but the information competes with itself leading to a dilution of distractors (Benoni & Tsal, 2010; Tsal & Benoni, 2010; Wilson *et al.*, 2011; Benoni & Tsal, 2012).

Other researchers even state that VWM capacity is defined by attentional control (Engle *et al.*, 1999; Kane *et al.*, 2001). Kane and colleagues (2001) quantified the individual VWM capacity by conducting an operation word span task (OSPAN) in

which participants had to solve mathematical operations while memorizing words. The test allowed to group participants into low span and high span performers based on their OSPAN performance. Afterwards a visual task was conducted, in which a cue was presented followed by a target either in the same location (prosaccadic) or in a different location (antisaccadic). Both span groups showed the same performance in the prosaccadic condition but differed in the antisaccadic condition. The low span group made more errors and was slower in the antisaccadic condition than the high span group, showing differences in attentional control that are related to capacity differences.

Impact of Visual Working Memory on Selective Attention What these theories have in common is, that selective attention is the mechanism that defines the contents that are processed by VWM, but there is also evidence that internal representations guide selective attention (Desimone & Duncan, 1995; Downing, 2000; Soto *et al.*, 2005; Olivers *et al.*, 2006, see Kiyonaga & Egner, 2013 for an overview). For example the previously described biased competition model (Desimone & Duncan, 1995) proposes that we have a bias towards information that is needed to follow our current goals and the focus of attention is guided to this relevant information by its representation in VWM. A study by Soto and colleagues (2005) goes beyond this assumption and proposes, that our internal representations can even guide attention to irrelevant information. In this study a visual search task was combined with a VWM task. An object was presented whose features (color and shape) had to be remembered. After a delay a search array was shown with a varying numbers of objects containing vertical lines. One of these lines was either tilted to the right or to the left and participants had to report the direction of this target line by button press. In some of the trials the prime object was probed to secure correct maintenance. The paradigm consisted of three conditions: a valid condition with the memory object containing the tilted target line, an invalid condition with the memory object containing a vertical distractor line and a neutral condition in which none of the objects in the search array matched the mem-

ory object. Reaction times were speeded in the valid trials compared to the neutral trials and were decreased when the memory object contained a distractor line (invalid trials). These results provide strong evidence that our memory representations can guide attentional capture even to irrelevant information.
To get a better understanding of how VWM and selective attention interact on a neural level, it is inevitable to consider the underlying neuromodulation by neurotransmitters involved in these processes such as dopamine and acetylcholine.

1.4 Neuromodulation of visual working memory and selective attention

1.4.1 Neurotransmitter acetylcholine

The first neurotransmitter, that was discovered, was acetylcholine which emerges in the central and peripheral nervous system and plays an important role in the autonomic nervous system where it is involved in sympathetic and parasympathetic processes (Dale, 1914, 1937). Acetylcholine is synthesized from choline and acetyl-CoA by the choline transferase. When this enzyme is present in a neuron it is referred to as "cholinergic" (Čolović *et al.*, 2013). Acetylcholine asserts its effect on neurons via muscarinic and nicotinic receptors. Nicotinic receptors react alongside acetylcholine - as the name indicates - to nicotine and are ionotropic, which means stimulation of this receptor takes a direct effect onto a neuron. Muscarinic receptors are metabotropic and have an indirect effect via a second messenger. Acetylcholine as well as muscarine, a poison that occurs in mushrooms, can stimulate this receptor type.
Acetylcholine is synthesized in a number of neurons in the brain and distributed via different pathways. Cholinergic neurons from the basal forebrain project to different parts of the cortex. Further cholinergic neurons originate in the septohippocampal nucleus and project to the hippocampus or originate in the pons forming inputs to

the thalamus and cortex. Apart from these pathways acetylcholine is found in many interneurons in the brain.

Two facts were leading to the assumption that attentional deficits observed in patients suffering from Alzheimer's disease (AD) are related to degeneration of cholinergic neurons in the basal forebrain: First, lesions in the basal forebrain result in attention deficits as shown in studies on monkeys (Voytko *et al.*, 1994) and rats (Turchi & Sarter, 1997). Second, degeneration of neurons in the nucleus basalis Meynert, a structure in the basal forebrain is observed in AD and is leading to a decrease of acetylcholine (Mesulam, 2004). Indeed it was directly shown, that the degree of damage in cholinergic neurons in the basal forebrain is correlated with cognitive deficits that are seen in AD (Perry *et al.*, 1978; Bierer *et al.*, 1995). Furthermore, drugs that inhibit the acetylcholine degrading enzyme cholinesterase enhance cognitive processes like attention (Furey *et al.*, 2007). It was assumed, that cholinergic neurons improve the signal to noise ratio for neural processes in primary sensory areas (Sillito & Kemp, 1983; Murphy & Sillito, 1991) but the clear mechanisms remain unclear. Evidence for this theory comes from an fMRI study of Furey and colleagues (2000) who modulated the acetylcholine level by the cholinesterase inhibitor physostigmine. Participants, performing a VWM task, showed increased neural activation when task relevant stimuli were presented but decreased activity when distractors were presented. This engagement of cholinergic processes in memory tasks was attributed to the attentional component of those tasks. In a study modulating cholinergic neurons by using nicotine gums in non-smokers, participants had to perform a classical posner task in the MRI (Thiel *et al.*, 2005). After treatment, reaction times were decreased in trials in which the cue was invalid requiring reorienting of attention. These results were accompanied by an increase of neural activity in left PC and precuneus. Note that effects in this study are restricted to nicotinic receptors which mainly exist in higher sensory brain areas as the PC, whereas muscarinic receptors are mainly distributed in primary sensory areas (Mentis *et al.*, 2001; Herrero *et al.*, 2008). In a review summarizing the results of animal (lesion, drug infusion and local acetylcholine release) and human (brain imag-

ing) studies it was shown that the cholinergic modulation of attention can mainly be observed in prefrontal, parietal and, visual areas (Klinkenberg *et al.*, 2011).
Because the exact role of acetylcholine in attention and its effects in the brain are not clear more studies on this issue are necessary to get a better understanding of diseases associated with cholinergic depletion like AD, Lewy body disease, schizophrenia etc. (Jellinger, 2000; Raedler *et al.*, 2006).

1.4.2 Neurotransmitter dopamine

Dopamine is a biogenic amine that emerges during the biosynthesis of adrenaline by hydroxylation of the amino acid L-Tyrosin and decarboxylation of Dihydroxyphenylalanin (L-Dopa, Blaschko, 1952). It is mainly synthesized in the central nervous system and transported via dopamine receptors and transporters. Five dopamine receptors are known, which are grouped into a D_1 receptor (D_1, D_5) and a D_2 receptor family (D_2, D_3 and D_4) based on their postsynaptic effects (e.g. Sibley & Monsma Jr, 1992; Civelli *et al.*, 1993). Binding of dopamine to a receptor of the D_1 family results in increasing cyclic adenosine monophosphate causing a depolarization of the respective neuron (Gorelova & Yang, 2000). Binding to a receptor of the D_2 family results in the opposite effect leading to a cyclic adenosine monophosphate mediated hyperpolarization (Neves *et al.*, 2002).
Dopaminergic neurons are known to be organized in different processing pathways in the brain namely the nigrostriatal, mesolimbic, mesocortical and tuberoinfundibular pathways (e.g. Seamans & Yang, 2004; Dunlop & Nemeroff, 2007). The nigrostriatal pathway is limited to the basal ganglia. Dopaminergic neurons of this pathway originate in the substantia nigra and project to the striatum. The mesolimbic and mesocortical pathways rise in the same brain region - the ventral tegmental area - but project to different parts of the brain. Whereas neurons of the mesolimbic pathway project to the limbic system via the nucleus accumbens, neurons of the mesocortical pathway straddle a longer distance to the PFC. Neurons of the tuberoinfundibular pathway originate in the hypothalamus and project to the pituitary gland. The

dopaminergic pathways are not only defined by projections to different parts of the brain but also by different functions. Whereas the tuberoinfundibular pathway modulates the secretion of the hormone prolactin, the nigrostriatal pathway is involved in movement control. The mesolimbic system is also known as the "reward system" because of its role in development of positive emotions and the mesocortical pathway is involved in executive functions. The dopamine receptors are not evenly distributed over all dopaminergic brain regions with the D_1 receptors mainly occurring in the PFC (Sawaguchi & Goldman-Rakic, 1991).

The assumption of an involvement of dopamine in working memory came up when it was shown that neural activity in PFC sustains during the delay period of a working memory task (Fuster, 1973; Brozoski *et al.*, 1979). In the following years this idea was confirmed by several pharmacological and lesion studies as well as by the better understanding of several diseases (Chao & Knight, 1995; Durstewitz *et al.*, 2000; Seamans & Yang, 2004; Cools *et al.*, 2007). A landmark in research on the role of dopamine in working memory was a number of experiments with monkeys conducted by Sawaguchi and Goldman-Rakic (1994). While the monkeys attended to a certain spot on a display, another spot was cued shortly in a location in the peripheral visual field. After a delay the fixated spot disappeared and the monkeys had to move the eye to the former cued location. Prior injected dopamine antagonists into the dorsolateral PFC induced different behavioral results. Injection of dopamine antagonists that were selective to receptors of the D_1 family (SCH 23390, SCH 39166) resulted in higher reaction times and lower accuracy whereas injection of dopamine antagonists leading to an inhibition of D_2 receptors (sulpiride, raclopride) had no behavioral effects. The results of these experiments were leading to the assumption that the dopamine involvement in VWM processes via the PFC is mainly modulated by receptors of the D1 family. Further research on this topic revealed that the representation of goal relevant information in memory is strengthened via dopaminergic modulation in PFC (Durstewitz *et al.*, 2000; Seamans & Yang, 2004; Cools *et al.*, 2007).

Since the basal ganglia play a major role in VWM processes and are innervated by dopaminergic neurons, the involvement of dopamine in VWM processes seems to be obvious as well. Indeed a relationship was shown by Kori (1995), who induced lesions in the caudate nucleus of monkeys leading to an impairment in memory guided saccades. Alongside the stabilization of goal relevant information via modulation in the PFC, dopamine seems to mediate the orienting and updating of information via modulation in the basal ganglia (Gruber *et al.*, 2006; Cools *et al.*, 2007). People suffering from Parkinson's disease (PD), which is characterized by a depletion of dopamine due to the degeneration of dopaminergic neurons in the basal ganglia, are mainly striving with motor control. Nevertheless the disease is accompanied by severe cognitive deficits in several domains like planning, working memory, attentional set shifting, language skills etc. (e.g. Levin *et al.*, 1992; Dubois & Pillon, 1996; Cools *et al.*, 2001; Pillon *et al.*, 2003). Medication with the dopamine precursor levodopa or dopamine receptor agonists leads to an improvement of motor control but to ambiguous results in terms of memory performance. Cools and colleagues (2009) tested patients suffering from PD, that were off and on medication, with a delayed matching-to-sample and a digit span test and compared their performance to those of healthy controls. Patients without treatment performed better in ignoring distractors in the delayed matching-to-sample task in comparison to the controls but showed impairments in the digit span task. These behavioral differences between patients and controls were suspended by dopaminergic medication. The authors concluded, that the differences in performance in both tasks stem from different involvement of basal ganglia and PFC in whereby dopamine in the basal ganglia are decreased, but increased in the PFC (Cools *et al.*, 2009; Cools & D'Esposito, 2011).

Despite the fact, that dopamine seems to modulate different aspects of VWM depending of the brain area that is involved, the individual baseline level of dopamine seems to play an essential role in memory processes as well. In several studies it was shown that the individual VWM capacity seems to rely on different baseline dopamine levels (e.g. Kimberg *et al.*, 1997; Kimberg & D'Esposito, 2003). In a study using the dopamine ag-

onist pergolide, participants with a higher verbal memory capacity benefited from the drug whereas participants with a lower span showed a poorer performance (Kimberg & D'Esposito, 2003). The same authors conducted a study with the selective dopamine agonist bromocriptine, only binding at D_2 receptors, and found a paradox effect (Kimberg *et al.*, 1997). Participants with a low span outperformed participants with a high span after taking the drug. These somehow controversial results were shown in many studies using different drugs (e.g. methylphenidate (Ritalin), haloperidol, bromocriptine, dextroamphetamine etc.) to modulate dopamine levels in the brain (Luciana & Collins, 1997; Mehta *et al.*, 2000; Mattay *et al.*, 2000; Gibbs & D'Esposito, 2005). A model that accounts for these ambiguous results is the "inverted U-function" model of dopamine (Cools & D'Esposito, 2011). The model proposes an optimal baseline level of dopamine, that is necessary for normal performance. Imbalance of this optimal level is leading to disruption in the memory process, depending on the task at hand. However, the exact role of dopamine during memory processes and its modulation via drugs is still not clear. Other researchers even propose an essential role of dopamine in attentional processes (Furey *et al.*, 2000; Robbins & Roberts, 2007).
With regard to several diseases in which imbalance of dopamine levels plays an essential role, like PD, schizophrenia, depression, drug abuse, restless leg syndrome etc., research on the exact function of this neurotransmitter is needed to get a better understanding of these diseases and improve treatments.

1.5 Genetical background of visual working memory and selective attention

Alongside lesion and drug studies, further contributions to the involvement of acetylcholine and dopamine in certain cognitive aspects are coming from studies investigating the genetic background of neurotransmission. Research on genetic polymorphisms (different variants of a certain gene) is helpful in understanding the role of cholinergic and dopaminergic neurotransmission in attention and VWM processes.

1.5.1 Cholinergic polymorphism: CHRNA4

As mentioned above, acetylcholine plays an essential role in attention processes. Genes and corresponding different variants of this genes (polymorphisms) coding for certain components of the cholinergic system can have an influence on cholinergic neurotransmission and even on behavior. A number of polymorphism in a certain gene came into the focus of research, coding for the $\alpha 4$ subunit of the nicotinic $\alpha_4\beta_2$ receptor (CHRNA4). A single nucleotide polymorphisms of this gene (rs1044396) characterized by the substitution of the base cytosine (C) with thymine (T) was associated with performance in attention tasks (Parasuraman *et al.*, 2005; Espeseth *et al.*, 2010; Greenwood *et al.*, 2009a). Parasuraman and colleagues (2005) conducted a study in which participants had to perform a Posner paradigm with letters. After a cue a letter was presented and participants had to decide whether the letter was a vowel or a consonant. In trials containing valid cues participants showed a benefit reflected in lower reaction times with higher numbers of C-alleles and a reduction of reaction time costs in invalid trials. Oppositional effects were found in a study using visual search and multiple object tracking (Espeseth *et al.*, 2010). In the visual search task participants had to search for a target letter (i.e. X or Z) presented among other non-target letters, circularly arranged around a central presented distractor letter. The trials could be either congruent (i.e. target X, center X) or incongruent (i.e. target Z, center X) and varied in load by non-target letters sharing either one or more features with the target letter. Participants with homozygot T-allele in the CHRNA4 polymorphism showed better performance in terms of accuracy and reaction times in high load trials in comparison to C-allele carriers. The same participants absolved a multiple object tracking task consisting of a presentation of twelve dots of which a number of two to six was marked as a target. After a few seconds the dots started moving for ten seconds and then stopped. At this point participants had to indicate the actual position of the cued targets by clicking on the corresponding positions in the display. In line with the results from the visual search task carriers of the homozygote T-allele performed better with increasing dot number which was interpreted by the authors as a higher tracking

capacity. An attempt to get a better understanding of these conflicting results might come, by taking a look at the inverted U-function of dopamine (p. 22). It is possible that acetylcholine follows the same mechanisms leading to different results depending on different cholinergic baseline levels and different task demands but a similar mechanism has not been found. Nevertheless, although these results are inconsistent they undoubtedly point to an involvement of the CHRNA4 gene in attentional processes.
The neural correlates of the effects of CHRNA4 polymorphisms are scarcely known. Winterer and colleagues were one of the first researchers who investigated this topic using fMRI and a visual oddball task (Winterer *et al.*, 2007). In this task a series of similar or same stimuli is presented with deviant stimuli in between, which have to be detected. In the study of Winterer participants had to respond to non-targets as well as to targets by button press. Effects of gene polymorphisms (rs1044396) were found in supplementary motor area (SMA), anterior cingulate cortex and left PC. Effects of gene dose were only found in left PC with increasing signal with higher numbers of the T-allele.
Despite the involvement of CHRNA4 polymorphisms in attention, these gene variants are found to interact with other variants asserting an effect on other processes like working memory (Markett *et al.*, 2010). Investigating the effects of a CHRNA4 polymorphism (rs1044396) and three dopamine receptor (D_2 family) polymorphisms (rs1800497, rs6277, rs2283265) during a VWM task, an interaction was found between the gene variants during high VWM load. The results of this study show, that it is insufficient to interpret the effects of one polymorphism on behavioral and neural changes without considering the influence that different neurotransmitter systems assert over another.

1.5.2 Dopaminergic & noradrenergic polymorphism: DBH

The dopamine-β-hydroxylase (DBH) is an enzyme, that is involved in the biosynthesis of noradrenaline by the chemical conversion of dopamine to noradrenaline. The occurrence of DBH is determined by the DBH gene coding for this enzyme. Different

variants of this gene are known that are resulting in varying enzymatic activity. A well-studied substitution of the base guanine (G) to adenine (A) on the DBH gene ($G^{444}A$) results in lower enzymatic activity associated with the A-allele (Cubells *et al.*, 1998, 2000). That means the ratio of noradrenaline to dopamine is shifted in favor of dopamine in A–allele carriers.

It is unknown in which areas of the brain DBH is active but it is likely that DBH is synthesized in those neurons that are involved in the synthesis of noradrenaline. Noradrenaline is mainly synthesized in the locus coeruleus which neurons are projecting to all parts of the cortex, the thalami, hippocampus, hypothalamus and the bulbus olfactorius.

The effects of the DBH polymorphism on behavior in working memory tasks were only shown by one research group (Parasuraman *et al.*, 2005; Greenwood *et al.*, 2009b). In the study from 2005 an allele dependent behavioral modulation was observed in a delayed matching-to-sample paradigm. Participants had to memorize the position of a varying number of one to three black dots that were randomly displayed on a screen. After a delay a red dot was presented either on the same position as one of the targets or on a different position and participants had to respond by button press if the red dot matched a target position. Behavioral differences were seen in conditions with the highest memory load (three dots) reflected in increasing accuracy with increasing G-allele. The same pattern could be observed in overall reaction time benefits. The authors interpreted these effects on working memory performance as a result of modulated dopaminergic transmission in the PFC relying on DBH-labeled fibers that were found post mortem in prefrontal brain areas (Gaspar *et al.*, 1989). In a subsequent study a similar paradigm was used: One black dot was preceded by a cue that consisted of a circle with varying size cuing the target location (Greenwood *et al.*, 2009b). After a delay again a red dot was presented that could either be in the same position as the target dot or in a different position. In non-match trials the distance between target and probe was also varied. Variation of cue size (precision) was seen as modulation of visual spatial attention, whereas modulation of target-probe distance

was seen as memory modulation. An interaction was observed with G-allele carriers showing the best performance during a large cue and the worst during the smallest cue. The interaction was reported for match and non-match trials during the shortest target-probe-distance. The results suggest rather an involvement of DBH in attention than in memory processes but were interpreted as an interaction effect between both processes.

Further studies on the possible involvement of DBH polymorphisms in working memory have to be made and one should always keep in mind that effects of these polymorphisms are rather due to noradrenergic modulation than to dopaminergic, because DBH is mainly synthesized in noradrenergic instead of dopaminergic neurons.

1.5.3 Dopaminergic polymorphism: COMT

The catechol-o-methyltransferase (COMT) is an enzyme that breaks down dopamine. Because dopamine transporters are rarely expressed in the cortex, dopaminergic transmission in this part of the brain is assumed to be mainly modulated by catabolic enzymes such as COMT (Garris *et al.*, 1993; Chen *et al.*, 2004). A gene coding for COMT can occur with different variants leading to a difference in enzymatic activity. In this polymorphism the base guanine (G) can be substituted by adenine (A) leading to an altered amino acid codon ($Val^{158}Met$) resulting in a marked decrease of enzymatic activity in COMT with the Met-allele (Chen *et al.*, 2004). Because of the occurrence of COMT in PFC and the low occurrence of dopamine transporters in this brain area, it is assumed that the COMT gene influences PFC activity. However, a direct influence has not been shown yet.

The role of dopamine during VWM processes is supported by effects of the COMT polymorphism on performance during VWM tasks (e.g. Egan *et al.*, 2001). While performing an n-back task (2-back and 0-back) participants in an fMRI study showed decreased PFC activity with increasing MET-allele (Egan *et al.*, 2001). Controversially, if the dopamine level is increased by dextroamphetamine (inhibition of monoaminergic transporters, release of dopamine and norepinephrine) or tolcapone (inhibition of

COMT) PFC activity is higher in Met-allele carriers than in Val-allele carriers during an n-back memory task (Mattay *et al.*, 2003; Apud *et al.*, 2006). These conflicting results can be explained by the "inverted U-function" model of dopamine (Cools & D'Esposito, 2011) assuming different individual baseline levels of dopamine (p. 22). Participants which were homozygote for the Met-allele showed an impairment in performance in a 3-back task after administration of amphetamine in the study of Mattay and colleagues (2003), suggesting an imbalanced dopamine level. Val-allele carriers did not show any behavioral effects after administration of amphetamine but showed an increased activity in PFC which can be interpreted as a shift of the dopamine level to an optimum leading to stronger neural responses (Clark & Noudoost, 2014). Conflicting results in the previously described study can also be due to different task demands. Whereas the task demands were low in the study of Egan and colleagues (Egan *et al.*, 2001), task demands were high in the study of Mattay and colleagues (2003). In addition to VWM processes, the COMT polymorphism is indirectly involved in attention processes. This association is known from studies on patients suffering from attention deficit hyperactivity disorder. However, whereas some researchers associate the Val-allele with this disorder (Eisenberg *et al.*, 1999), other researchers propose the Met-allele as a risk allele (Sun *et al.*, 2014).

1.6 Effects of age on visual working memory and selective attention

Alongside neurotransmitter level differences based on genetic variation, a decline of neurotransmitter function can be observed during healthy aging (Li & Rieckmann, 2014) leading to impairments in working memory and attention processes. In addition, healthy aging is associated with a loss of cortical thickening and metabolic activity which can also lead to cognitive decline.

Evidence for a dopaminergic deficit in healthy aging accumulated in the last years of research. For example Erixon-Lindroth and colleagues (2005) observed a reduction

of positron emission tomography (PET) ligand binding potential (a marker for the density of a receptor or transporter) of presynaptic dopamine transporter in the striatum in healthy elderly. A reduction of binding potential in D_2 receptors in striatum were found by Kaasinen and Rinne (2002). Similar results were found for D_1 and D_2 receptors (Suhara *et al.*, 1991; Kaasinen *et al.*, 2000), pointing to the fact that the whole dopaminergic system seems to be affected during aging. Becaue of the previously discussed role of dopamine in cognitive processes like working memory it is conjecturable that dopaminergic deficits in healthy aging result in cognitive deficits. Indeed several studies have shown an association. In a study combining PET and fMRI, healthy participants performed a listening span task to measure VWM capacity and a delayed recognition task to measure accuracy and response times of trials with a high or low memory load (Landau *et al.*, 2009). In addition, dopamine synthesis capacity was measured in the striatum via PET. Alongside the finding that dopamine synthesis in caudate nucleus correlated with VWM capacity and dopamine synthesis in putamen correlated with response times the authors reported a link between caudate dopamine, brain activation and behavioral estimates. Participants that had a high caudate dopamine synthesis showed an activation increase in left inferior frontal junction during increased memory load and performed better in the delayed recognition task. The authors interpreted the inferior frontal region as a brain area playing an essential role in the integration of working memory processes. In another study, PET markers reflecting caudate D_1 receptor density were used to show that reduced receptor density in elderly is correlated with a reduction of frontoparietal connectivity in comparison to younger participants (Rieckmann *et al.*, 2011).

The number of non-invasive methods that can be used to measure dopamine levels in vivo are limited. Alongside PET the measurement of magnetization transfer (MT) during structural imaging can be used as well. By means of MT from immobile protons that are bound in macromolecules to mobile protons the density of macromolecules in certain natural tissues can be assessed (Wolff & Balaban, 1989), allowing conclusions about the structural integrity of neural systems. In a study of Düzel and collegueas

(Düzel *et al.*, 2008) the structural integrity of the dopaminergic substantia nigra and ventral tegmental area was positively correlated with performance in a verbal memory task in elderly.

The age related decline in neurotransmitter levels reported here can also be observed in terms of other neurotransmitters like acetylcholine. Results of several studies point to a reduction of cholinergic muscarinic (Dewey *et al.*, 1990) and nicotinergic receptors (Mitsis *et al.*, 2009). The degeneration of cholinergic neurons in aging is supposed to be caused by a lack of trophic support (see Schliebs & Arendt, 2011 for an overview). Studies directly combining non-invasive measurements of cholinergic levels in the brain with cognitive performances are rare.

While there is a lack of studies investigating the direct relation between neurotransmitters and cognitive deficits in healthy aging, a huge body of literature deals with the cognitive deficits and underlying neural correlates associated with aging. By conducting a meta-analysis over 30 research reports that tested young and elder participants in a working memory or inhibition task, Turner and Spreng (2012) created brain maps showing activity patterns that were common for each age group during the mentioned tasks. During working memory tasks elderly showed decreased activation in IPS, insula and FEF and increased activation in frontal brain areas (MFG, IFG), SMA and IPS in contrast to young participants. During inhibition tasks elderly participants showed a decrease in activation in OCC and an increase in frontal brain areas only (medial (MFG), inferior (IFG) and superior frontal gyrus). The increase of frontal brain activity during memory and filtering processes in elderly was interpreted as a compensation mechanism (Reuter-Lorenz & Cappell, 2008) reflecting a need for increased cognitive control. A reduction of cognitive control in elderly was also shown in a study testing young and elder participants in a memory task consisting of faces and scenes (Gazzaley *et al.*, 2005a). The participants were instructed to either attend to faces or scenes and to ignore stimuli of the other category. In addition, a task was included in which scenes or faces were viewed passively. The authors expected to find an increase in brain activation in the face processing area (FFA) when faces

were attended in comparison to the passive viewing task whereas a decrease was expected when faces had to be ignored. The same results were expected for scenes in the place processing brain area (PPA). In young participants the hypothesized effect was observed for scenes in PPA only. In the elderly an increase was seen in PPA but no decrease in response to ignored scenes which was in addition reflected in impaired memory performance. The authors interpreted these results as a lack of suppression ability in response to irrelevant information in elderly. The cognitive deficits seen in elder participants were often compared with deficits in children (Hasher & Zacks, 1988; Sander *et al.*, 2011). However, current findings reveal slight differences between the inhibition deficits in children and elderly. In an EEG study it was shown that inhibition suppression in elderly is not abolished during aging but seems to be delayed resulting in longer response times (Gazzaley *et al.*, 2008). These results were reaffirmed by a study of Jost and colleagues (2011) using a delayed matching-to-sample task in which relevant and irrelevant stimuli were presented in one array in comparison to the task used by Gazzaley (2008).

The previously reported studies reveal insights into the pharmacological and neural background of healthy aging but leave a number of questions unanswered. The direct pharmacological mechanisms that are leading to inhibition deficits in elder participants are not fully understood. The fact that cognitive deficits in elderly resemble cognitive inabilities in children only on the surface needs further assessment. A common method in evaluating interventions to improve cognitive deficits in elderly is to test these interventions in young participants before, which might be misleading because of different underlying mechanisms. A better understanding of the neural and pharmacological mechanisms leading to cognitive deficits in healthy aging would lead to a change in developing interventions.

2 Objectives and hypotheses

Although a huge body of scientific literature is dedicated to working memory and attention and the interaction of both processes respectively, still little is known about the exact mechanisms and underlying neural correlates. The main aim of this thesis was to shed more light onto the interaction of working memory and selective attention, the underlying neural correlates and moreover, the role of the neurotransmitters dopamine and acetylcholine in this interplay. For that purpose, a delayed matching-to-sample paradigm was designed, based on the paradigms of McNab and Klingberg (2007) and Vogel and Machizawa (2004). The paradigm involved different memory and attentional loads whilst the perceptual load was kept constant. The paradigm consisted of three conditions with the first having high memory but no filtering demands, the second having low memory and low filtering demands and the last having low memory but high filtering demands (Fig. 2.1). This working memory and attention task, which is referred to as "'combined task"', was performed by a group of young and elderly healthy participants in the MR scanner to investigate the neural operations demanded by the task, namely working memory and attention processes.

2.1 Definition of memory and filter correlates

In the memory and attention task participants had to memorize either four rectangles or two. In trials, in which only two rectangles had to be memorized, two additional rectangles were presented as distractors, which had a different orientation than the target rectangles. The distractors could either have the same color as the target

or a different color so that the attentional demand differed between conditions. A cue indicated whether all four targets had to be memorized or only two. The array containing the rectangles was succeeded by a probe which could be on a position formerly occupied by a target, by a distractor or by no rectangle at all.

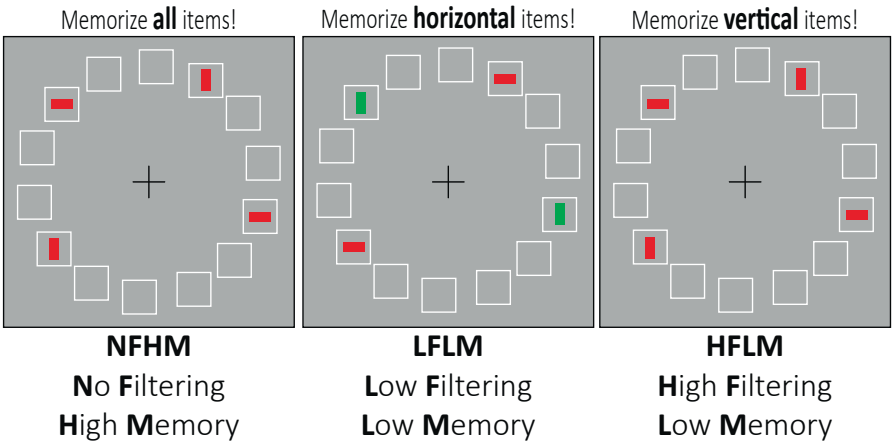

Figure 2.1: Schematic illustration of the sample display from the paradigm used in the present thesis

Hit rates and corresponding response times of each condition served as behavioral measures of working memory and attention performance. In addition, filtering ability in form of correct rejections and corresponding response times, when the probe was on a position formerly occupied by a distractor, was assessed. As an indirect measure for memory performance the memory deficit was used, which is defined by the difference between performance in the low memory (low filtering) condition and the high memory (no filtering) condition whereas large values indicate that participants were impaired when memory load was increased (Fig. 2.2). Similarly as an indirect measure for the

filtering ability served the difference in performance between the condition with a low memory and filtering load and the condition with a low memory but high filtering load. These assumptions were made based on the hypothesis, that performance should be best in the low demanding memory and attention condition and worse in the high demanding conditions. If distractors were correctly ignored, performance in the low memory but high demanding filtering condition should be similar to performance in the easy condition (low memory, low filtering demands). Hence, it follows that a low

filter deficit would imply a good filtering ability. In addition, mistakenly memorized distractors as targets in both distractor conditions would lead to an increased number of false alarms as well as slower response times.

With regard to the neural correlates of working memory and selective attention processes, contrasts of parameter estimates were defined from the encoding period of the fMRI task reflecting both processes separately. A contrast between the high memory load condition and the low memory but high filtering condition was referred to as memory contrast, whereas the inverse contrast was referred to as filter contrast. These contrasts were chosen deliberately between these two conditions without including the low memory and filtering load condition, because the visual input in these conditions was exactly the same only the task that had to be completed differed (Fig. 2.1). Memorizing distractors in the high filtering condition should lead to an unnecessary increase in activity in storage related brain regions whereas activity can be "'spared"' when distractors are succesfully ignored. For that purpose, activity differences from the memory contrast were referred to as "'effective storage activity"' (Fig. 2.3). Brain regions showing stronger activity differences in the memory contrast were expected to be the PC and prefrontal regions. As outlined before, the PC constitutes a likely candidate for memory storage based on findings of lesion studies (Baldo & Dronkers, 2006; Finke *et al.*, 2006) and fMRI studies using different tasks (for an overview see Rottschy *et al.*, 2012). The PFC (especially the dorsal part) was also expected to emerge during the memory contrast because of its role as a control region and its involvement in the storage of spatial information (Goldman-Rakic, 1987; Rottschy *et al.*, 2012).

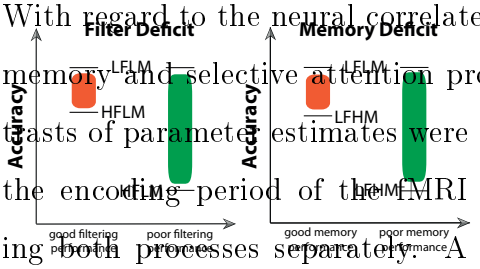

Figure 2.2: Model of individual differences in filtering reflected in memory related accuracy

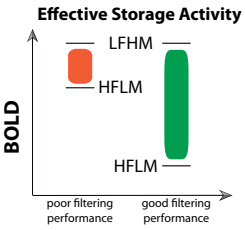

Figure 2.3: Model of individual differences in filtering reflected in memory related BOLD response

Regarding the filter contrast a more extensive net of co-activated regions was expected to emerge. Frontostriatal regions, including the PFC with its role in information

control (Pessoa *et al.*, 2003; Corbetta & Shulman, 2002; Pessoa & Ungerleider, 2004; Postle, 2005; Lepsien & Nobre, 2006; Burgess *et al.*, 2007a,b) and the basal ganglia which are found to be involved in information filtering (McNab & Klingberg, 2007) were expected to emerge. Certain brain regions of the ventral and dorsal attention network described by Corbetta and colleagues (2002) were also expected to be found in the filter contrast. Activity differences from the filter contrast were referred to as filter activity (Fig. 2.3).

2.2 Influence of working memory capacity on memory and filter correlates

As discussed in the previous chapter, it is well known that the individual VWM capacity depends on the ability to filter out irrelevant information. Support for this thesis comes from EEG studies showing that an electrophysiological marker – the CDA, reflecting the amount of information stored in memory - differs between participants based on the individual filtering performance (Vogel & Machizawa, 2004; Vogel *et al.*, 2005). FMRI studies verified these findings by reporting brain activity in a certain region, namely the PC, showing similar patterns as the CDA (Todd & Marois, 2005). Also the connection between memory related brain activity and individual filtering performance was shown by fMRI studies (McNab & Klingberg, 2007). Nevertheless, in former studies memory and attentional load were often confounded with perceptual load, so that increasing memory and attention demands were associated with increasing perceptual demands. As mentioned before, the paradigm used in this thesis was developed to cope with these irregularities by keeping the perceptual load constant. Another pitfall of former studies is the assessment of individual VWM capacity from the same task from which inferences about memory and filtering performances were made, posing a circular analysis. To circumvent this issue, a separate VWM capacity task was conducted with all participants several days prior to the fMRI measurement and the individual VWM capacity was calculated based on performance in this task.

In terms of behavioral markers correlations of the hit rate and response times were expected to occur with VWM capacity calculated from performance in the separate task. Also with regard to the findings of Vogel and colleagues (2004; 2005) associations between VWM capacity and behavioral measures of filtering ability are conceivable. BOLD activity differences of storage related brain regions were expected to correlate with measures of memory performance in the combined task but especially the PC to correlate with filtering measures and the individual VWM capacity. Participants with a high VWM capacity were expected to show a better filtering ability. This should be reflected in a low filter deficit and a more accurate rejection of the distractor as well as in larger activity differences in brain regions of the memory contrast. Smaller activity differences in the PC during the memory contrast would indicate the same amount of memorized items, including the distractors in the low memory/high filtering load condition. If markers of filtering ability are reflected in storage related regions, this would be a clear hint in what sense memory processes and attentional processes are connected. Especially a connection between the direct measure of filtering performance (correct rejection) would be a strong and new proof of an interaction between both processes.

2.3 Influence of drug administration and genetic diversity on memory and filter correlates

Another focus in this thesis was made on the neurotransmitters dopamine and acetylcholine that are known to be involved in memory and filtering processes. Dopamine seems to be a modulator of working memory processes which was shown by several lesion (e.g. Chao & Knight, 1995) and pharmacological studies (Durstewitz *et al.*, 2000; Seamans & Yang, 2004; Cools *et al.*, 2007). In patients suffering from PD, which is characterized by a dopaminergic deficit, administration of dopamine modulating drugs resulted in an improvement of memory function. In contrast, acetylcholine is more involved in filtering processes (Thiel *et al.*, 2005; Furey *et al.*, 2007). Results

of the majority of studies on that topic are leading to the assumption, that the roles of dopamine and acetylcholine seem to be clearly separated to working memory and attention, but there are also some inconsistencies. Memory deficits in AD, which is characterized by a lack of acetylcholine, for example are treated with cholineesterase blockers that are increasing the level of acetylcholine in the brain. Furthermore, a few studies are showing an improvement of memory performance after cholinergic modulation (e.g. Furey *et al.*, 2000). Dopamine on the other hand seems to be an essential modulator of frontostriatal brain regions that are known to be relevant for filtering of irrelevant information instead of memory processing (Robbins & Roberts, 2007). Because of these inconsistent results and to achieve a better understanding for the treatment of diseases characterized by dopaminergic and cholinergic lacks, pharmacological modulation of the mentioned neurotransmitters was part of this thesis. By administering either the dopamine precursor levodopa or the cholineesterase blocker galantamine prior to the fMRI session, effects of these neurotransmitters on working memory and attention processes during the delayed matching-to-sample task could be investigated. Levodopa was expected to increase performance in the high memory load condition whereas galantamine was expected to improve the filtering ability of participants in those conditions demanding filtering. Stronger effects were expected to occur in the elderly in contrast to the younger participants due to a lack of these neurotransmitters during healthy aging. These behavioral effects should be reflected either in an activity decrease in involved brain regions due to compensational effects or in an increase because of a better recruitment of necessary brain regions. The modulation effects should be supported by genetic differences reflected in different polymorphisms. Storage related differences should be found in participants with variants of the dopaminergic genes DBH and COMT and filtering related effects in participants with variants of the cholinergic CHRNA4 gene. These assumptions were made based on genetic studies that found performance differences in working memory tasks for DBH and COMT polymorphisms carriers and in attention tasks for CHRNA4 polymorphism carriers (Egan *et al.*, 2001; Parasuraman *et al.*, 2005).

Behavioral and neural differences were also investigated with regard to the structural facilities of the brain. Therefore, volume of the dopaminergic innervated substantia nigra and the cholinergic innervated basal forebrain were assessed. In addition, MT measurements of these structures were included to get an indirect measure of structural integrity of the mentioned brain regions. Participants with a lower volume or higher MT ratio were expected to benefit more from the neurotransmitter modulation than participants with higher structural values. These effects were expected to occur essentially in the cohort of elderly participants. It was shown before that the structural integrity of the mentioned brain regions seems to be correlated with performance in those regions in elderly (Düzel *et al.*, 2008). Moreover, healthy aging is accompanied by a decline of neurons and therefore neurotransmitter function (Li & Rieckmann, 2014). Hence, stronger effects of neurotransmitter modulation are expected to occur in elderly participants mainly. In addition, decline in filtering as well as memory performance is expected to occur as reflected in higher response times and lower accuracy in this age group.

3 Methods

3.1 General procedure

Participants were recruited by means of advertisements in local newspapers and public notices. A first screening testing for exclusion and inclusion criteria (section 3.2) was executed via structured email correspondence and phone interviews. Participants who met the criteria for the study were invited to a first session (T1) on which a detailed screening was executed (Fig. 3.1). Alongside the collection of psychological and neuropsychological data and the investigation of individual VWM capacity, blood samples were taken by medical staff for genetic analysis on the first session. Elderly participants practiced the task which was later performed in the MR scanner on the first meeting for 20 minutes. After an interval of several weeks the second (T2) and third (T3) session took place on which the participants performed the same memory and filtering task on both days in the MR scanner. Both MRI sessions were conducted in a period of maximum ten days but with a minimum interval of two consecutive days. Before each fMRI session either a placebo or a drug (levodopa/ galantamine) was administered. Drugs were administrated in a double-blinded crossover design except from the group of elderly which received galantamine/placebo single-blinded because of organizational reasons. In addition to the

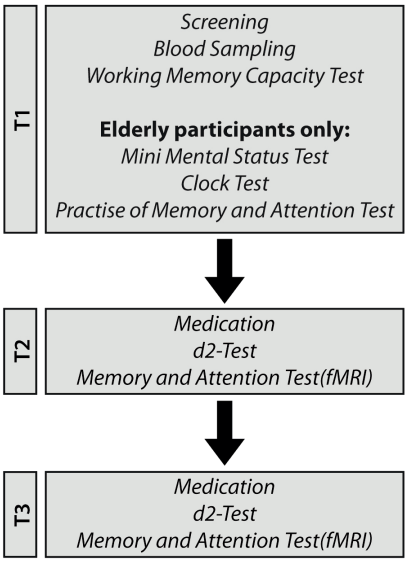

Figure 3.1: Overview of study procedure

previous mentioned tests, the general concentration ability was examined via the d2-test.

This study was approved by the local ethics committee of Otto-von-Guericke University. All participants were paid volunteers and gave written informed consent before participation.

3.2 Inclusion and exclusion criteria

Only healthy, right handed participants with normal or corrected-to-normal vision in the age of 20-35 and 60-75 were included. To reduce the probability of cognitive deficits in the cohort of elderly only those participants were allowed to participate which reached a score over 27 in the mini mental status test (MMST, see section 3.4.1 for test description). Excluding criteria for the measurement in the MR scanner were metallic implants, implanted electrical devices (e.g. pacemakers), tattoos, surgery on vessels, tinnitus, seizures or claustrophobia. Contraindications in respect to levodopa and galamtanine were allergies against components of the drugs, angle-closure glaucoma, pregnancy/breast-feeding, phaeochromocytoma, treatment with monoamine oxidase blocker or a severe liver or kidney disease. Data were excluded from the analysis in case of under 55 % correct responses in one of the task conditions in the attention and memory task. Elder participants whose performance did not reach 55 % in the training were excluded from all following measurements.

3.3 Participants

Suitability of 55 young (age 26.31 ± .36 standard error of the mean (SEM), range 21 - 33) and 103 elderly participants (age: 66.30 ± .44 SEM, range 59 - 75) was determined in a detailed screening. In the end, data of 40 out of 54 young and 38 out of 77 elderly who performed the combined task in the MR scanner could be used for analysis. This strong loss of participants was due to different causes such as not

meeting the inclusion criteria, poor performance, technical problems, claustrophobia or excessive movement when lying in the scanner (Tab. 3.1). In addition, the very tight head coil in the Siemens Verio MR scanner made a measurement over a long period for participants with a big circumference of the head in combination with the MR glasses impossible. When the elderly participants were measured with prior administration of non-retarded galantamine, four out of fourteen participants were suffering from severe nausea so series of measurements were immediately stopped and the non-retarded galantamine that was used without any side effects in the young cohort was replaced with retarded galantamine for the elderly participants. The valid measurements of seven out of the fourteen previously measured participants were not included in any analysis and the new series of measurement was started with administrating retarded galantamine only. Five participants had to be excluded from the group of young participants because of a performance under the level of 55 % during the MRI experiment, whereas ten participants in the group of elderly had to be excluded due to this reason.

Table 3.1: Overview of the number of participants that was excluded because of exclusion criteria

not meeting inclusion criteria			invalid fMRI data		
Reason	**Young**	**Elderly**	**Reason**	**Young**	**Elderly**
Non-retarded galantamine group	-	14	Claustrophobia	-	3
Smoker	-	1	Incidental finding	1	1
Antidepressant	1	-	Ineligible head size	-	4
Tinnitus	-	1	Performance in session 1 $<$ 55 %	5	10
Magnetic implants	-	2	Technical problems	1	2
Visus $>$ 8	-	4	Vertigo	1	-
Participants request	-	2	Participants request	4	2
MMST $\leq$ 27	not collected	3	Strong movement	2	2
Trainings performance $\leq$ 55%	not collected	12	Uresiaesthesia	-	2
Sum	**1**	**39**	**Sum**	**14**	**26**

The levodopa group consisted of 20 participants (6 female) in the age between 21 and 29 years (M = 25.80 $\pm$ 0.53 SEM) and 20 participants (11 female) in the age between 58 and 74 years (M = 65.79 $\pm$ 1.06 SEM). The order of administration and the corresponding sample size can be depicted from Tab. 3.3. Both age groups were comparable in terms of gender distribution ($\chi^2 = 2.558$; df = 1; p = .110). Exact age, body mass index (BMI), a measure for the relation between body height and weight,

and mini mental score (elderly only) for those participants whose data were actually analysed can be depicted from Tab. 3.2. A univariate analysis of variance (ANOVA) revealed a significant difference in age (F(1,27.649) = 1122.775, p = .000) between both levodopa groups but not for the BMI (1,38) = .583, p = .450).

Table 3.2: Demographic composition of sample: Means and SEM for age, BMI and MMST (elderly only) from participants of each drug group (levodopa/galantamine) and p-values of univariate ANOVAs reflecting group differences

	Group Levodopa/Placebo			Group Galantamine/Placebo		
	Young	Elderly		Young	Elderly	
	Mean (SEM)	Mean (SEM)	p-Value	Mean (SEM)	Mean (SEM)	p-Value
Age	25.80 (.05)	65.79 (1.06)	**.000**	25.65 (.63)	65.82 (.90)	**.000**
BMI	22.85 (.90)	21.96 (.71)	.450	20.21 (.63)	21.16 (.62)	.237
MMST	-	29.21 (.16)	-	-	29.24 (.18)	-

The galantamine group (Tab. 3.2) comprised 20 participants (7 female) in the age between 22 and 32 years (M = 25.65 ± .063 SEM) and 18 participants (13 female) in the age between 61 and 73 years (M = 65.82 ±.90 SEM). Both age groups were not comparable in terms of gender distribution (χ^2 = 5.265; df = 1; p = .022) but in terms of BMI (F(1,36) = 1.410, p = .243). Both groups differed significantly in age (F(1,36) = 1471.558, p = .000). The order of administration and the corresponding sample size can be depicted from Tab. 3.3.

Table 3.3: Administration order and corresponding sample size for both age cohorts

fMRI Sessions Levodopa				fMRI Sessions Galantamine			
Session 1	Session 2	Young	Elderly	Session 1	Session 2	Young	Elderly
Levodopa	Placebo	12	11	Galantamine	Placebo	10	8
Placebo	Levodopa	8	9	Placebo	Galantamine	10	10

3.4 Psychological and neuropsychological questionnaires

All psychological and neuropsycholgical tests used in the present study were chosen in reference to inclusion and exclusion criteria (MMST) as well as for the purpose of testing cognitive functions (D2 Test).

3.4.1 Mini mental status test

The MMST (Folstein *et al.*, 1975) was developed for detection of cognitive deficits and comprises the tests of temporal and spatial orientation, memory, language and language comprehension, attention as well as constructional practice. The test is divided into nine task modules and a scale of points from 0 to 30. One point is assigned for every correct solved task. Following the IDC-10-GM-2014 (Graubner, 2013) participants reaching a value between 24 and 30 are having either no or a slightly cognitive deficit. Because the MMST Value is dependent on individual age and educational level, a score over 27 was defined as an inclusion criteria following the population based standard of Crum (Crum *et al.*, 1993).

3.4.2 D2 test

The D2 Test is a paper-pencil based version which has been proposed as a particularly useful measure of the individual attention and concentration performance (Brickenkamp, 1962). The tests consists of 14 rows filled with the letters "d" and "p", which have a number of one to four marks above and below. The participants task is to cross all "d's" with two marks in total (three alternative versions: $\overset{''}{d}\ \underset{''}{d}\ \overset{'}{d}\ \underset{'}{d}$). Each row, containing 47 letters, has to be processed in 20 seconds. Different values can be calculated for interpretation. The concentration performance (CP) was used for analysis, which is calculated by subtracting comission erros (CM, number of distractors that were canceled) from the total number of processed letters. This measure is known to be most resistant to falsification compared to other values from the d2 test. In addition, the raw error value (ER), comprising the sum of targets that were not canceled (omission error, OM) and the CM was calculated as a percentage of the total processed letters with the following formula:

$$ER = 100 * \frac{OM + CM}{TN} \tag{3}$$

3.5 Modulation of neurotransmitter levels and analysis of neurotransmitter differences

3.5.1 Genotyping

Blood samples (4 ml) were taken from every participant during the pretest for DNA analysis. The DNA extraction and analysis of individual gene polymorphisms was carried out by members of the department of behavioral neurology of the Leibniz institute for neurolobiology of Magdeburg. Genotyping of the $C^{1545}T$ polymorhism of the CHRNA4 gene (rs1044396), the $G^{444}A$ polymorphisms of the DBH gene (rs1108580) as well as the $Val^{158}Met$ polymorphism of the COMT gene (rs4680) were based on standard methods (Parasuraman *et al.*, 2005; Wimber *et al.*, 2011).

3.5.2 Drug administration

All drugs were provided and masked in a capsule by the pharmacy of the university hospital Heidelberg. Because of severe side effects (nausea and vomiting) after administration of non-retarded galantamine in elderly, the retarded variant, provided by a pharmacy from Magdeburg, was administrated single-blinded in a new sample.

Levodopa

L-Dopa (L-3,3-Dihydroxy-phenylalanine; Levodopa) is a preparation usually used for the treatment of PD by balancing the lack of dopamine that is characteristic for this disease. To prevent the decarboxylation of levodopa in extracerebral organs, levodopa is administered in combination with the decarboxylase blocker Carbidopa. For this study a single dosis of 100 mg levodopa (NACOM® 100, Janssen-Cilag GmbH) in combination mit 25 mg Carbidopa was orally given in form of a tablet. Because of a maximal levodopa plasma concentration after approximately 0,7 hours and an activity of two to four hours (based on pharmacokinetic data) levodopa was administered approximately one hour (Tab. 3.4) before the fMRI session started.

Galantamine

Galantamine is a preparation that is used for the treatment of dementia, especially AD. It increases the concentration of acetylcholine in the brain by means of a twofold mechanism of action. On the one hand galantamine is a selective, competitive and reversible blocker of the enzyme acetylcholineesterase, which hydrolyses acetylcholine to acetate and choline. On the other hand the intrinsic activity of acetylcholine on nicotinergic receptors is amplified by galantamine. For this study an 8 mg single dosis of galantamine (REMINYL®, Janssen-Cilag GmbH) was administered orally in form of a tablet. The non-retarded galantamine which was administered one hour (Tab. 3.4) before the fMRI session to the young participants is leading to a maximum concentration of galantamine after approximately one hour. Half of the active substance is depleted after approximately eight to ten hours (Reminyl Fachinfo). Because the retarded form of galantamine is reaching a maximum release of substance after four hours, the time between drug adminsitration and fMRI session start was increased to two hours (Tab. 3.4) for the elder participants.

Placebo

The capsules of placebos that were provided by the pharmacy of the university hospital Heidelberg contained filling material. The placebo capsules that were used in the galantamine group for elderly participants resembled the galantamine capsules and were composed of magnesium (Abtei Pharma Vertriebs GmbH).

Table 3.4: Mean exposure times and SEM between drug administration and fMRI session start (min); F- and p-values of repeated-measures ANOVAs reflecting group differences

	Levodopa	Placebo			Galantamine	Placebo		
	Mean (SEM)	Mean (SEM)	$F_{1,\ 19}$	p-value	Mean (SEM)	Mean (SEM)	$F_{1,\ 19}$	p-value
Young	66.85 (2.34)	67.90 (2.68)	.099	.757	70.25 (2.87)	66.00 (2.22)	1.223	.283
Elderly	72.25 (2.42)	71.75 (3.27)	.028	.869	130.00 (3.68)	127.22 (4.32)	.208[1]	.654

[1] F(1,17)

3.6 Experimental tasks

3.6.1 Working memory capacity task

Participants performed a computerized VWM capacity test a few weeks prior to fMRI sessions (Fig. 3.2).

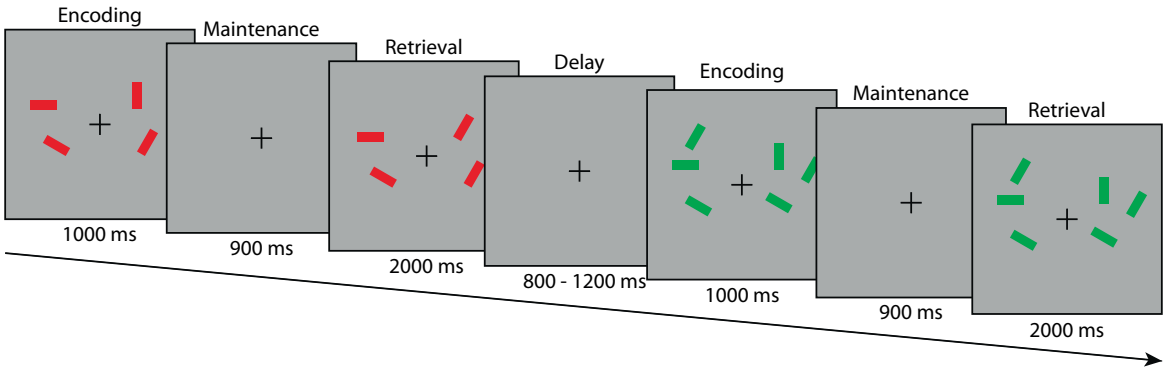

Figure 3.2: Schematic illustration of working memory capacity task

At the beginning of the test an instruction was shown, which indicated what button participants had to press. Participants had to detect a change in orientation of one rectangle out of a number of two to seven presented rectangles in the probe array compared to the memory array and report the presence or absence of a change by button press (right index- and middle finger). Changes in the array were present in 50% of the trials. To ensure that the participants understood the instruction, all participants completed one short practice session (eight trials) before participating in the main experiment. Stimuli were presented against a grey background (luminance 40 cd/m^2). Memory and probe stimuli were presented within two 7° x 12° rectangular areas that were centered 1° to the left and right of a central fixation cross. Participants performed 360 trials in which the number of two to seven green or red rectangles (size 0.6° x 2°) were presented randomized on each trial with the constraint that distance between two items was greater than 0.5°. In change trials one rectangle was turned by 0°, 30°, 60°, 90°, 120° or 150°. The memory array was presented for 0.1 s and was followed by a delay of 0.9 s. The probe array was presented for 2 s and followed by 0.8-1.2 s until the next trial started.

VWM capacity was calculated with a standard formula (formula 1, p. 11) for change detection tasks with a whole display (Pashler, 1988). The individual VWM capacity was then calculated by taking the mean between the capacities for two, three and four items.

3.6.2 Combined working memory and attention task

Participants participated in a computerized combined task during fMRI sessions (Fig. 3.3). At the beginning of each run an instruction was shown, which indicated what color the participants had to attend. A cue in form of a geometric shape (circle, triangle and square) linked with a certain task that was learned before scanning, appeared at the start of each trial. The three instructional cues resulted in three memory conditions that prompted the participants to voluntarily direct their attention to two or four of the presented rectangles. In one of the three main conditions a circle cue was followed by a memory array of either four red or four green rectangles. The circle indicated that participants had to memorize the positions of all four rectangles (**N**o **F**iltering, **H**igh **M**emory, NFHM). The second condition consisted of a square cue that referred to memorize only the horizontal rectangles. This cue was followed by a memory array with either two green horizontal and two red vertical rectangles or two green vertical and two red horizontal rectangles (**L**ow **F**iltering, **L**ow **M**emory, LFLM). In the third condition a triangle cue, linked with the task to only memorize the vertical rectangles, was followed by a memory array of either four red or four green rectangles of which two rectangles were horizontal, two vertical (**H**igh **F**iltering, **L**ow **M**emory, NFHM). On presentation of the probe stimulus participants were required to make a button press with the index or middle finger of their right hand, depending on whether a grey dot appeared on the same position of the previously memorized rectangles or not. When the probe stimulus was not in the position of a target, it was either on a distractor position (only LFLM or HFLM) or on a position adjacent to the target positions that was formerly an empty placeholder square ("background"). The required responses (yes or no) were distributed evenly across all trials.

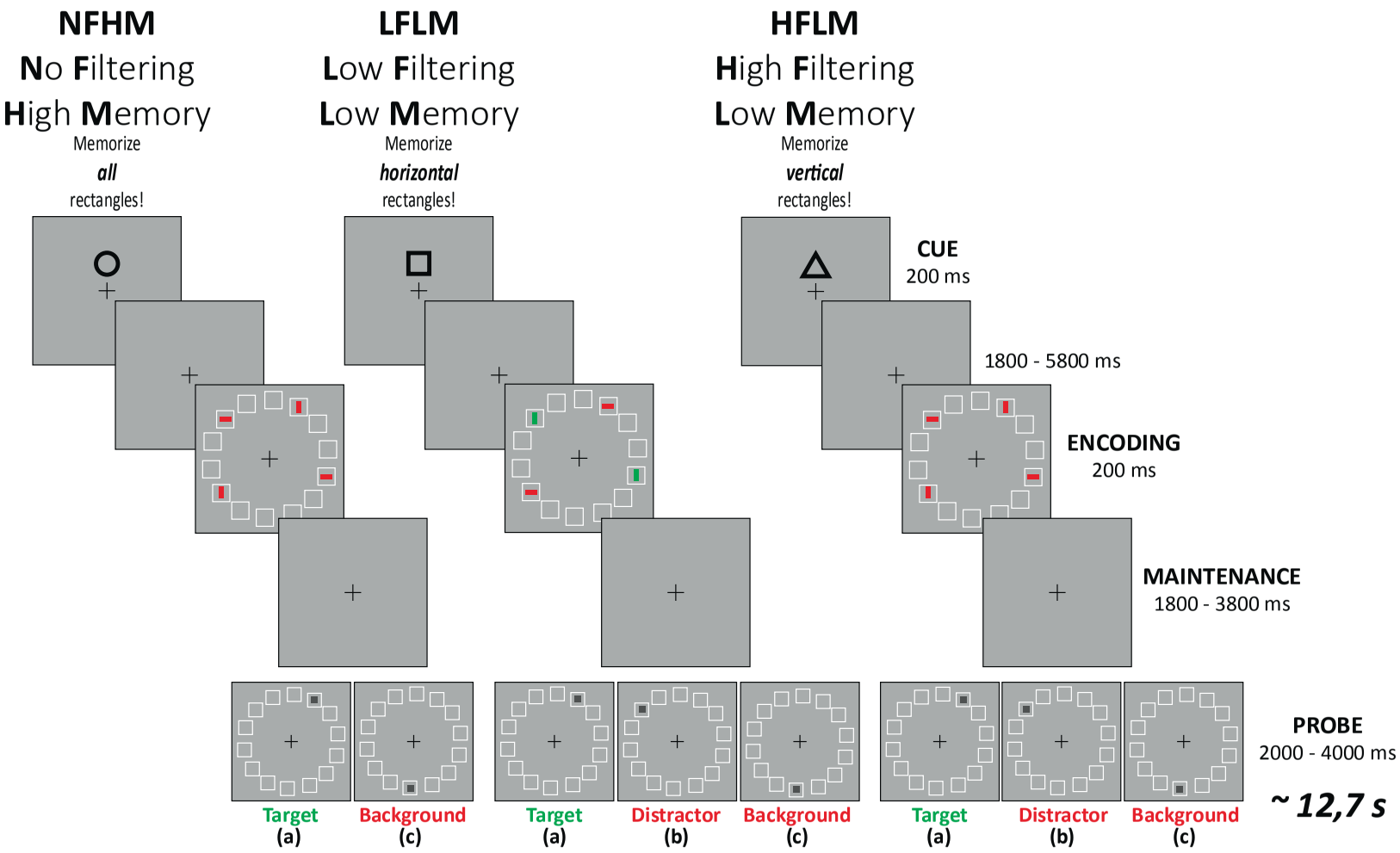

Figure 3.3: Schematic illustration of combined working memory and attention task

On 50% of the no responses in the LFLM and HFLM condition, the probe stimulus was on a distractor position and on 50% on an adjacent position to the target. Participants absolved 6 runs á 58 trials (348 trials in total). In order to exclude a possible bias to a certain stimulus color targets were presented in red in half of the runs and in green in the other half of the six sessions. Consequently distractors in the LFLM condition were red when targets were green and green when targets were presented in red. Before participating in the main experiment all participants completed one short practice session (12 Trials) outside the scanner.
Stimuli were presented against a grey background (luminance 41.2 cd/m^2). Cue stimuli (0.6°x0.6°) were presented 0.5° above a fixation cross that was placed in the center (16.4° from side, 18.8° from top). Sample and probe stimuli appeared within fourteen task irrelevant placeholder squares (size 0.9° x 0.9°) arranged in a circle (diameter 7.3°, minimum difference Squares: 1.5° center to center). Each sample array contained two horizontal and two vertical rectangles (size 0.8° x 0.3°) which appeared in four of the placeholder squares. The sample stimuli consisted of four red, four green or two green and two red rectangles (luminance: red = 31 cd/m^2; green = 34 cd/m^2). The probe stimuli contained a grey square (size 0.3° x 0.3°) which appeared in one of the placeholder squares. The instruction cues were presented for 0.2s and were followed by a delay of 1.8, 3.8 or 5.8 s. The sample array was presented for 0.2s and was followed by a delay of 1.8 or 3.8 s. All Trials ended with a probe stimulus that lasted for 1.4s and was followed by a delay of 0.6 or 2.6 s.

3.7 Apparatus: Magnet resonance imaging

3.7.1 Basic concepts of magnet resonance imaging

Magnet resonance imaging (MRI) is a non-invasive imaging method that is mainly based on the magnetic characteristics of hydrogen atoms. By means of a strong magnetic field hydrogen atoms, that are usually oriented randomly in the body, become equally aligned parallel or anti-parallel to the magnetic field. Because both orientations

are not balanced among hydrogen atoms and because hydrogen atoms are naturally rotating around their own axis (spin) producing a small magnetic field, aligned hydrogen atoms in an external magnetic field produce a net magnetization (longitudinal magnetization). In addition to the natural rotation around the own axis, hydrogen atoms in an external magnetic field rotate around the axis of this field (precession). The speed of this rotation (precession or larmor frequency) is dependent on characteristics of the atom as well as on the strength of the external magnetic field. A high radio frequency pulse (HF pulse) is then applied orthographic to the magnetic field to align all hydrogen atoms to one orientation so that the atoms rotate synchronized and absorb energy. Therefore it is necessary that the HF is in accordance with the precession frequency. After excitation via the HF pulse hydrogen atoms realign slowly in a rotating manner back to the alignment parallel to the magnetic field (relaxation). Thereby absorbed energy is emitted and can be detected by a receiver coil. The duration of relaxation is different depending on the measured tissue allowing to differentiate measured tissue based on the signal intensity. Tissues with high densities (e.g. brain tissue) have a faster relaxation of hydrogen atoms leading to stronger signal whereas density in the liquor for example is characterized by slower relaxation times and therefore lower signal intensities. MRI takes advantage of the different characteristics of relaxation times in different types of tissues and is therefore a strong diagnostic tool to identify tissue changes in the whole body due to certain diseases.

3.7.2 Experimental setting: Structural magnet resonance imaging

Because of technical reasons the different age cohorts had to be measured on separate MR scanners (Siemens Magnetom Trio and Verio) therefore information about both devices is provided in the next sections.

Magnetization transfer

The method of MT measurement was first introduced by Wolff and colleagues in (1989) and is based on the assumption of mobile and immobile protons in natural tissue. Immobile protons are bound in macromolecules and characterized by short T2-relaxation times (making these protons invisible in MR imaging) and by a broad larmor frequency spectrum. In contrast, mobile protons that are prevalent in water have long T2-Relaxation times and a narrow larmor frequency spectrum. The latter attribute is facilitating a stimulation of immobile protons only by a certain resonance frequency. If this frequency (off-resonance impulse) is leading to a saturation of magnetization in immobile protons magnetization is transferred to adjacent mobile protons and followed by a decrease of signal intensity that is known as "magnetization transfer". Because of different proton density in different tissue types (Wolff & Balaban, 1994) this imaging method can be used to visualize certain structures of the body. Whereas the highest MT ratios in the brain can be found in white matter which mainly consists of makromolecular myelin lower MT ratios are found in grey matter. Due to its big amount of mobile hydrogen protons the MT effect is not visible in liquor.

Structural MRI data acquisition

For the assessment of the MT ratio structural images were collected covering the whole brain with a T2*-weighted echo planar imaging (EPI) 3D gradient echo sequence (80 transversal slices, FoV 256 x 256 mm, Voxelsize 1 x 1 x 2 mm) for the elder participants on the Verio (Siemens Magnetom Verio syngo MR B19, Erlangen, Germany) and a 2D spin echo sequence (34 transversal slices, FoV 256 x 256 mm, Voxelsize 1 x 1 x 3 mm) for the young participants on the Trio (Siemens Magnetom Trio syngo MR A35, Erlangen, Germany). The images consisted of a MT image with a magnetic saturation pulse and an image (noMT image) without this saturation pulse (Fig. 3.4). After coregistration of the noMT image into the MT image to align both images onto each other a new MT ratio image was created by a voxel based calculation of formula

4.

$$MTRatio = \frac{noMT - MT}{noMT} \tag{4}$$

Grey values of regions of interest (ROIs) were read out from the MT ratio images. In addition, volumes of ROIs were calculated that were corrected for the individual total brain volume (TBV) by dividing the ROI volume by TBV. TBV values were calculated from a MP-RAGE sequence (96 sagittal slices, thickness = 2 mm, FoV 256 x 256 mm, no gap, spatial resolution = 1 x 1 x 2 mm, TI = 1100 ms; Trio: TR = 1650 ms, TE = 5.01 ms; Verio: TR = 1660 ms, TE = 5.05 ms) by adding the volumes of white matter, grey matter and cerebro spinal fluid using the SPM8 software package (Welcome Department of Cognitive Neurology, University College London, UK) and MATLAB R2009b (The Mathwork Inc.).

ROI analysis: Substantia nigra

The substantia nigra ROI, that was visually dissociable from surrounding structures because of its contrast, was segmented on transversal MT images in 3-4 slices using MRIcro (Rorden & Brett, 2000) (Fig. 3.4).

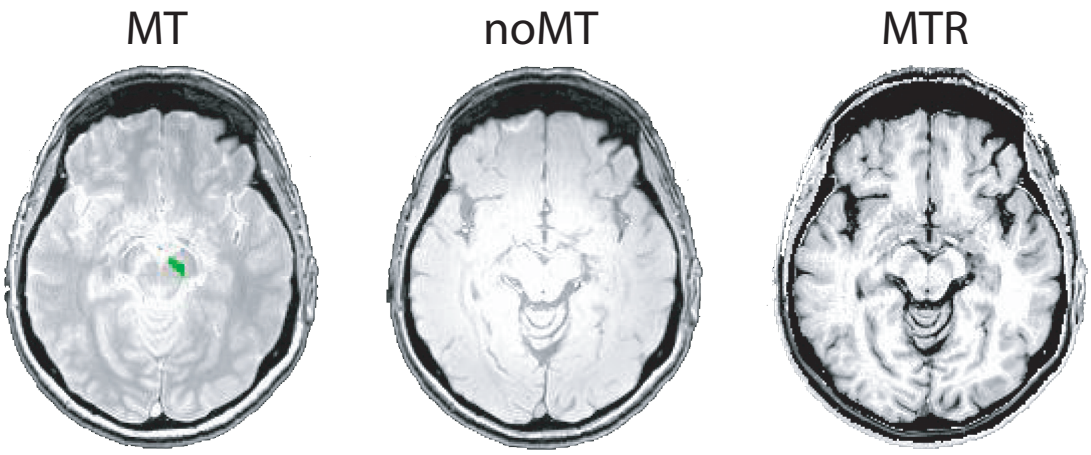

Figure 3.4: Transversal slices of MT, no MT and MT ratio image with right Substantia nigra ROI on MT image

ROI analysis: Basal forebrain

Subregions of the basal forebrain cholinergic system were defined using Mesulams nomenclature (Mesulam *et al.*, 1983a,b, 1988). These regions included cholinergic cells associated with the medial septal nucleus, vertical and horizontal limb of the diagonal band of Broca and the nucleus basalis Meynert. Masks of the basal forebrain cholinergic system were assessed by a cytoarchitectonic map that was created by a combination of histology and MRI of a post mortem brain of a non-demented 56 year old man (Grinberg *et al.*, 2007). The map was transferred into Montreal Neurological Institute (MNI) standard space and used to read out basal forebrain volumes from individual MP-RAGE images (96 sagittal slices, thickness = 2 mm, FoV 256 x 256 mm, no gap, spatial resolution = 1 x 1 x 2 mm, TR = 1650 ms, TE = 5.01 ms, TI = 1100 ms). Assessment of basal forebrain volumes was carried out by members of the working group "clinical dementia research" from the DZNE Rostock and is described in detail in (Kilimann *et al.*, 2014). Due to the external assessment of basal forebrain volumes no ROIs were available to asses individual MT ratios of the basal forebrain.

3.7.3 Basic concepts of functional magnet resonance imaging

Whereas MRI techniques are used to investigate structural changes in the body functional MRI (fMRI) is a method to study neural activity that is due to sensory, motor and cognitive processes in the brain. The technique of fMRI is mainly based on the hemodynamics in the brain and the BOLD response which was described by Ogawa and colleagues (Ogawa *et al.*, 1990). Whenever neurons are active, energy in the form of adenosine triphosphate is required which is provided by the oxygenation of glucose. The oxygen is provided by hemoglobin (Hb) molecules in the blood that are changing to deoxygenated hemoglobin (doHb) after emitting the oxygen. Because of the emission of oxygen in doHb, the iron molecules that are part of the Hb contain unpaired electrons that are leading to a small magnetic field, that is influencing the spin of surrounding hydrogen protons. As a consequence when oxygen is consumed

the increasing amount of doHb is leading to a decrease in signal intensity. To ensure the sufficient supply of active neurons with oxygen the cerebral blood flow is increased around those neurons. As a result the amount of doHb is decreasing and the amount of oxygen containing hemoglobin (oHb) is increasing. Because oHB is not magnetic (diamagnetic) the local signal increases again. The difference in signal intensities caused by changing amounts of doHb and oHb is known as BOLD contrast. The link between changes in neural activity and changes in cerebral blood flow is called neurovascular coupling and is still not exactly understood. An attempt to shed more light into this issue was made by Logothetis and colleagues (Logothetis *et al.*, 2001). The authors compared local field potentials, single cell and multi unit recordings with BOLD responses in the visual cortex of macaques. As a result local field potentials that are reflecting the synaptic input were the best predictors of the BOLD response. Another issue in addition to the unknown biological processes behind neurovascular coupling is the supply of oHb containing blood to broader regions than needed. Consequentially the measured signal change does not reflect the metabolic needs per se but rather the increased blood supply. When interpreting fMRI results one has to keep in mind that the BOLD contrast is a measure of changes in regional cerebral blood flow instead of a direct measure of neural activity.

3.7.4 Experimental setting: Functional magnet resonance imaging

fMRI data acquisition - Siemens Trio

A 3 Tesla MR scanner (Siemens Magnetom Trio syngo MR A35, Erlangen, Germany) equipped with an 8-channel head coil was used to measure BOLD brain activity in young participants. Stimuli were back-projected by a LCD projector on a screen positioned behind the coil. The screen was viewed by the participants via a mirror attached to the head coil. Functional images were acquired with a T2*-weighted EPI gradient echo sequence in an odd-even interleaved sequence (FoV 224 x 224 mm, voxel

size = 3.5 x 3.5 x 3.5 mm, TR = 2000 ms, TE = 29 ms, flip angle = 80°). Thirty-four 3.5mm thick axial slices (64 mm x 64 mm in plane, no gap) parallel to the AC-PC line were acquired for 255 volumes in each run. Whole-head T1-weighted images were collected with a MP-RAGE sequence (96 sagittal slices, thickness = 2 mm, FoV 256 x 256 mm, no gap, spatial resolution = 1 x 1 x 2 mm, TR = 1650 ms, TE = 5.01 ms, TI = 1100 ms).

fMRI data acquisition - Siemens Verio

fMRI data of elderly participants were collected using a 3 Tesla MR scanner (Siemens Magnetom Verio syngo MR B19, Erlangen, Germany) equipped with a 32-channel head coil. A LCD projector was used to back-project stimuli on a screen positioned behind the coil. The screen was viewed by the participants via a mirror attached to the head coil. Functional images were collected using thirty-two axial slices (64 mm x 64 mm in plane, no gap) covering the whole brain with a T2*-weighted EPI gradient echo sequence in an odd-even interleaved sequence (FoV 224 x 224 mm, voxel size = 3.5 x 3.5 x 3.5 mm, TR = 2000 ms, TE = 38 ms, flip angle = 80°). Axial slices were acquired parallel to the AC-PC line for 255 volumes in each run. Whole-head T1-weighted images were collected with a MP-RAGE sequence (96 sagittal slices, thickness = 2 mm, FoV 256 x 256 mm, no gap, spatial resolution = 1 x 1 x 2 mm, TR = 1660 ms, TE = 5.05 ms, TI = 1100 ms).

fMRI data analysis

Data processing was performed using the SPM8 software package (Welcome Department of Cognitive Neurology, University College London, UK) and MATLAB R2009b (The Mathwork Inc.), which included slice timing, realignment to the first volume, coregistration to individual anatomical image, normalization to the MNI template (Friston *et al.*, 1995) and resampling into a voxelsize of 3 x 3 x 3 mm^3. Spatial normalized images were smoothed with an isotrophic 6 mm FWHM Gaussian kernel and highpass filtered (cut-off 128 s). Global scaling was applied across an individual ses-

sion to remove global signal drifts before GLM analysis. No participants had to be excluded because of excessive head motion (more than 5 mm). BOLD responses were modeled by delta functions at the time of stimulus onsets. For each individual, the time courses of the hemodynamic BOLD responses in the different conditions (NFHM, LFLM and HFLM) were analyzed at the voxel level using a linear regression model that yielded separate time courses for the cue phase, encoding phase and response phase of a condition. The movement parameters derived from the realignment process were included as covariates into the model (Friston et al. 1998) as well as all trials in which the participants made a wrong response leading to 16 regressors in total for each run (Cue phase: NFHM, LFLM, HFLM; Encoding phase: NFHM, LFLM, HFLM; Response phase: NFHM, LFLM, HFLM; errors; 6 x movement parameters). To identify regions activated by attentional filtering and memory storage, respectively, we calculated different contrasts of parameter estimates for each participant and each session individually for each condition in the encoding phase (NFHM, LFLM, HFLM) in a first-level analysis and used the contrast images of every participant for the definition of memory and filtering correlates in a random effects second-level analysis. Contrasts from the first level analysis of all placebo sessions were subjected to a ANOVA (3 x 2 full factorial design) for each age group separately to assess whether the two placebo groups of each age group differed in terms of BOLD during the task. In a second step a one-way within ANOVA (rANOVA) with the within subject factor task (NFHM/LFLM/HFLM) and the time point of measurement (first/second session) as covariate was carried out for each age group. To define brain regions which are specificly involved in memory and filtering processes the contrasts HFLM $>$ NFHM to identify filter related areas (referred to as "filter contrast") and the contrast NFHM $>$ HFLM to reveal memory storage related brain regions (referred to as "memory contrast") were calculated. All cluster peaks within significant activation clusters with a minimum distance of 18 mm and a minimum cluster extend of 10 contiguous voxels are reported in MNI standard space using an auxiliary voxel-level threshold of $p<0.005$ (uncorrected) with subsequent cluster-level correction for multiple testing at $p<0.05$

(false discovery rate (FDR) corrected). Activation maps were visualized using the MRIcro software package (Rorden & Brett, 2000) and projected on the ch2bet template which is included in the software package. Brain regions were defined by using the n30r83 maximum probability brain atlas (Hammers *et al.*, 2003; Gousias *et al.*, 2008) which is based on MR images of 30 healthy participants in the age of 20 to 54 and is provided on www.brain-development.org. The atlas includes 83 brain regions that were manually delineated.

ROI analysis:

For a more detailed analysis of functionally defined clusters, ROIs were defined by intersecting activated brain regions of the calculated group contrasts with a sphere (5 mm radius) centered at the peak voxel of each cluster via the MarsBar toolbox implemented in SPM8 (Brett *et al.*, 2002). ß-values of all ROIs were extracted from the data of each participant for each condition (NFHM, LFLM, HFLM) and the time interval of interest (encoding phase) and subjected to various ANOVAs for further analysis.

3.8 Statistical analysis

Analysis of all behavioral, structural and functional MRI data was carried out by means of the statistical software package SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Descriptive statistics were reported in form of mean and SEM. In case of graphical visualization of results, histograms were used with bars picturing the mean and error bars picturing one SEM in positive and negative direction. Outliers were identified using box plots. Statistical significance was declared in case of a p-value $< .05$. Significant differences are indicated with one asterisk in case of a p-value $< .05$ and with two in case of a p-value $< .01$.

When the ANOVA sphericity assumption was violated according to Mauchly's test, the Greenhouse-Geisser correction was applied and adjusted F- and p-values were reported. Similarly if homogeneity of variance was violated, F- and p-values were adjusted. Significant main effects were followed by pairwise comparisons (Bonferroni corrected if necessary).

For all analyses except the anaylsis of drug effects (section 4.3) only those sessions were used in which a placebo was administrated before. Data of placebo groups were collapsed for each age cohort separately to increase statistical power. For that purpose differences between placebo groups were analyzed as a first step by including "placebo group" as a between factor in terms of ANOVAS or covariate in terms of correlation analyses. In case of significant differences between placebo groups, the between factor "placebo group" was included for all further analyses. In the following sections the statistical tests used for every data type are listed.

3.8.1 *Statistical analysis:* Definition of memory and filtering correlates

Behavioral data: Memory and attention task

For the analysis of performance (% correct and response times) in the memory and attention task hit rates were assessed. In addition to hit rates, correct rejection rates were calculated from trials in which the probe was on a position former occupied by a distractor (LFLM and HFLM), to investigate whether irrelevant information was memorized. As an indirect measure for the individual filtering ability (filter deficit) the difference of hit rates between condition with a weak (LFLM) and a strong (HFLM) distractor was calculated. The individual difference between the hit rates in condition with high (NFHM) and low (LFLM) working memory load was used as an indirect measure for the memory ability of the participants (memory deficit). Only data of those sessions were used for analysis in which placebo was administrated before.

All previous mentioned performance measures were subjected to different ANOVAS: Response types (hit rates, correct rejections and corresponding response times) were separately analyzed with repeated-measures ANOVAS (rANOVA) including the within subject factor "task" (NFHM/ LFLM/HFLM) and the between factor "placebo group" (levodopa placebo group/ galantamine placebo group). Univariate ANOVAS were further carried out on filter and memory deficit with the same within and between subject factors. As placebos were administered in half of the participants prior to the second session because of the cross over design of the study the order of measurement (first/second session) was included as a between subject factor. In case of no significant main effect of placebo group or task x placebo group interaction data of both groups were collapsed an subjected to succeeding rANOVAs with the within subject factor "task" and the between subject factor "session" to assess whether different memory and attention demands in the delayed match to sample paradigm had an influence on the performance of participants. Comparative analyses of age group data were performed including "age" as a between subject factor (young/elderly).

Functional MRI Data: Memory and attention task

Extracted ß-values from all ROIs that were defined in the filter and memory contrast were subjected to a rANOVA with the within subject factors "region" and "task" for the collapsed data of placebo groups of each age cohort separately. In case of significant main effects of region subsequent rANOVAs with the within subject factor "task" were carried out for each region separately. Because contrasts were controlled for the order of measurement as the second level analysis was carried out, this factor was not included into the analysis.

Interaction of behavioral filtering performance and storage related BOLD activity

For further analysis the ß-value differences between the NFHM and the HFLM condition were calculated from ROIs of the memory contrast. This index is referred to as

"effective storage activity". To investigate whether behavioral memory and filtering performance was reflected in BOLD differences in storage related brain areas, effective storage activity of ROIs from the memory contrast was correlated with markers of behavioral performance (hit rates, correct rejections, filter and memory deficits) by means of a partial correlation with order of measurement (first/second session) as a covariate.

Structural MRI data: Substantia nigra and basal forebrain

MT ratio of substantia nigra (SN_{MT}) as well as volumes of subtsantia nigra (SN_{vol}) and basal forebrain (BF_{vol}) were subjected to a univariate ANOVA with the between factors "placebo group" and "session" for each age cohort separately. MT Ratios and volumes of subtantia nigra could not be assessed in two participants of the elder cohort so analysis was carried out with a sample of n = 36.

Effects of structural integrity on performance in combined task

The influence of structural measures in behavioral performance in the memory and attention task was assessed for each age cohort separately by partial correlations including the order of session (first/second session) as a covariate.

3.8.2 *Statistical analysis:* Influence of visual working memory capacity on correlates of storage and filtering

Behavioral data: Working memory capacity

To test for differences between placebo groups in each age cohort working memory capacities of different set sizes were subjected to rANOVAs with the within factor "set size" (two to seven) and the between factor "placebo group" (dopamine placebo group/galantamine placebo group). The between subject factor "placebo group" was included in all further analyses on VWM capacity if differences between placebo groups were found to be significant. Data of collapsed placebo groups were subjected to a

succeeding rANOVA with the within factor set size. For the purpose of investigating capacity differences related to age a rANOVA was carried out with both age cohorts and an additional between subject factor "age" (young/elderly).

Behavioral data: Effects of working memory capacity on performance in memory and attention task

To investigate in what sense performance in the combined task is dependent on the individual VWM capacity hit rates, correct rejections, filtering and memory deficits were correlated with individual VWM capacity that was measured in the pretest and calculated as the mean capacity of set size three, four and five. By means of partial correlation the data were controlled for the order of measurement, by including "session" (first/second session) as a control variable.

Functional MRI data: Effects of working memory capacity on neural correlates of memory and attention

Effective storage activity and filter activity of the collapsed placebo group data were correlated with VWM capacity for each age cohort separately to link brain activation with individual memory limitations. Because contrasts were controlled for the time of measurement, "session" was not included in the analysis.

Structural MRI data: Effects of structural integrity on working memory capacity

Associations between VWM capacity and MT ratio or volume of substantia nigra and basal forebrain were assessed by partial correlations.

3.8.3 *Statistical analysis:* Influence of drug administration on correlates of storage and filtering

Behavioral data: Effects of drug administration on performance in memory and attention task

To test the influence of drug administration on performance in the memory and filtering task (hit rate, correct rejection, memory and filter deficit), rANOVAS with the within subject factors "drug" (placebo/levodopa; placebo/galantamine) and "task" (NFHM/ LFLM/HFLM) were carried out for each age cohort and each drug group (levodopa/galantamine) separately. The time point of drug administration (first/ second session) was included in the analysis as a between subject factor accounting for the crossover design of the study. For the purpose of investigating age effects additional rANOVAS were carried out for each drug group separately with the additional between factor "age" (young/elderly).

Behavioral data: Effects of working memory capacity on drug effects in memory and attention task

To test whether drug effects were dependent on VWM capacity participants were divided into groups of participants with a low and high VWM capacity by median split for each drug group. rANOVAs were carried out with the within factor "drug" (dopamine/placebo or galantamine/placebo), the between factors "performance group" (low/high VWM capacity) and "drug session" (first/second session).

Functional MRI data: Effects of drug administration on neural correlates of memory and attention

Analysis of effective storage activity and filter activity by rANOVAs with the within subject factors "drug" (placebo/drug (galantamine/levodopa)) and "region" and the between subject factor drug session (first/second session) was carried out for each drug group of each age cohort separately to test the effects of pharmacological neurotrans-

mitter modulation. In case of significant drug effects further rANOVAS were carried out for each ROI separately.

Structural MRI data: Effects of structural integrity on drug effects in memory and attention task

RANOVAs on behavioral data with the within subject factor "drug" (levodopa or galantamine/placebo) and the between subject factor "drug session" (first/second session) on MT ratio or volumes of substantia nigra and basal forebrain were carried out to asses whether drug effects on behavioral data occurred in dependency on structural factors.

3.8.4 *Statistical analysis:* Influence of genetic diversity on correlates of storage and filtering

For analysis of polymorphisms effects participants were separated into allele groups *mm*, *mv* and *vv* for COMT *gg*, *ag* and *aa* for DBH and *cc*, *ct* and *tt* for CHRNA4. Genetic data for CHRNA4 and DBH of one young participant were not available thus analysis was carried out with a sample of n = 39. In the cohort of elderly participants CHRNA4 polymorphisms could not be assessed in three participants whereas DBH and COMT could not be assessed in two participants thus analysis was carried out with a sample of n = 35 for CHRNA4 and n = 36 for DBH and COMT polymorphisms.

Behavioral data: Effects of genetic diversity on performance in memory and attention task

To test the influence of genetic diversity on performance in the memory and filtering task univariate ANOVAS with the within subject factor "task" (NFHM, LFLM, HFLM) and the between subject factor "gene" were carried out for each age cohort and each gene polymorphism separately. Correct rejections were analyzed separately with rANOVAS including the same factors. To account for the crossover design of

the study the time point of placebo administration (first/second session) was included in the analyses as a between subject factor. To investigate age effects additional rANOVAS were carried out for each gene polymorphism separately with the additional between subject factor "age" (young/elderly).

Behavioral data: Effects of genetic diversity on working memory capacity

Univariate ANOVAs were carried out on VWM capacity for each gene polymorphism as a between factor separately.

Functional MRI data: Influence of genetic diversity on neural correlates of memory and attention

Effective storage activity and filter activity were subjected to rANOVAs with the within factor "region" and the between factor "gene" for each polymorphism and each age group separately. In case of significant main effects of region, univariate ANOVAs were carried out for each region separately. Age effects were assessed by rANOVAs with the additional between factor "age" (young/elderly).

Structural MRI data: Effects of genetic diversity on structural integrity

To investigate structural differences based on genetic diversity univariate ANOVAS were carried out on SN_{MT} as well as on SN_{vol} and BF_{vol} with the between factor "gene" for each age cohort separately.

4 Results

In the following sections results of the conducted experiments will be presented. In the first section (4.1) behavioral and functional correlates of the combined task as well as structural correlates of brain regions involved in the synthesis of dopamine and acetylcholine are reported. In addition, interactions between functional and behavioral correlates as well as between behavioral and structural correlates were tested. To increase statistical power, data of placebo groups of each age cohort were collapsed and data were controlled for possible differences between placebo groups. In the next section (4.2) results of the VWM capacity test are reported and associations between this measure and previously described behavioral, functional and structural correlates are tested. This section is followed by a section reporting the effects of drug administration on behavioral, functional and structural correlates as well as effects of drug administration in dependency on VWM capacity (4.3). The last section of this chapter is about effects of genetic diversity on behavioral, functional and structural correlates as well as on VWM capacity (4.4).

4.1 Definition of memory and filter correlates

4.1.1 *Behavioral data:* Combined Task

Young participants

Means and standard errors are graphed in Fig. 4.1 and can be depicted from Tab.4.1 including statistical values. Analysis of hit rates by a rANOVA revealed neither a main

effect of placebo group ($F_{1,36}$ = .009, p = .927) nor a task x placebo group interaction ($F_{2,55}$ = 1.299, p = .275) thus data were collapsed over both groups. A succeeding rANOVA for the combined groups revealed a main effect of task ($F_{2,58}$ = 47.568, p = .000) and a significant task x session interaction ($F_{2,58}$ = 5.669, p = .010) but no significant main effect of session ($F_{1,38}$ = .967, p = .332). Post hoc multivariate ANOVAs on hit rates showed an effect of session in the high memory condition only ($F_{1,38}$ = 4.945, p = .032). Participants significantly improved performance in this condition from the first (77.56 % ± 2.23 SEM) to the second session (83.56 % ± 1.62 SEM). Both filtering conditions were not influenced by training effects (LFLM: $F_{1,38}$ = .006, p = .937; HFLM: $F_{1,38}$ = .347, p = .559). In general hit rate in the HFLM condition (87.93 % ± .99 % SEM) was significantly lower than in the LFLM condition (91.42 % ± .74 % SEM, p = .000) and lowest in the NFHM condition (80.86 % ± 1.41 % SEM, p = .000). Performance in both filtering conditions differed significantly (p = .000).

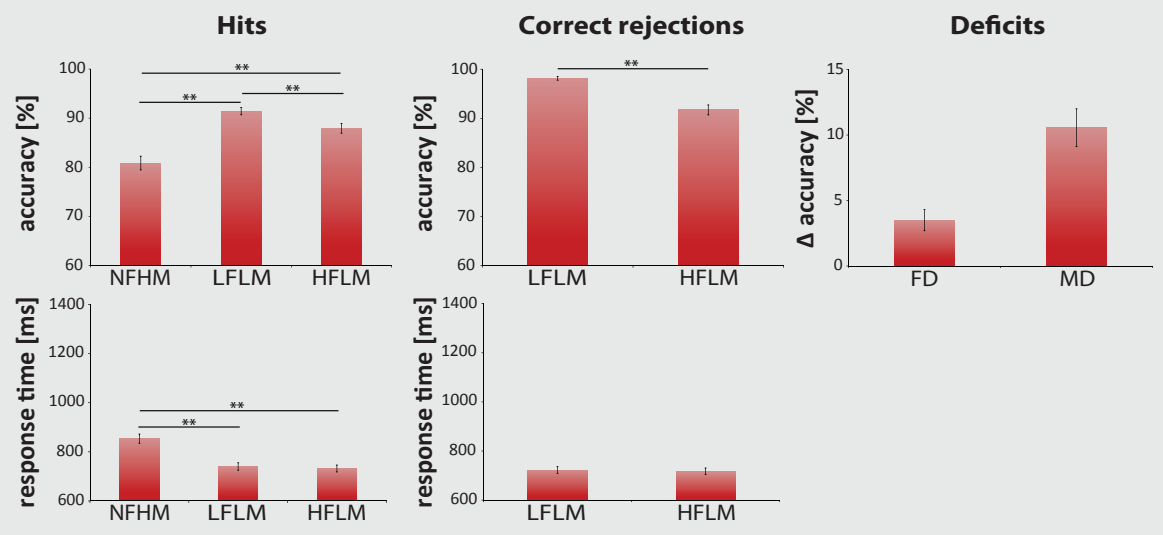

Figure 4.1: Performance of young participants in the combined task: *Left column:* Group-averaged hits (%) of all conditions and corresponding response times (ms); *Middle column:* Group-averaged correct rejections (%) of LFLM and HFLM condition referring to lure trials and corresponding response times (ms); *Right column:* Group-averaged filter and memory deficit (Δ%); error bars indicate the standard error of the mean

Analysis of response times corresponding to hit rates revealed neither a main effect of placebo group ($F_{1,36}$ = 1.490, p = .230) nor a task x placebo group interaction

($F_{2,56}$ = 1.870, p = .171) thus data were collapsed over both groups. A succeeding rANOVA for the combined groups revealed a main effect of task ($F_{2,58}$ = 165.445, p = .000). Participants responded significantly faster in both distractor conditions (LFLM: 740.19 ms ± 15.13 SEM; HFLM: 732.09 ms ± 14.28 SEM) than in the NFHM condition (853.70 ms ± 18.82 SEM, p = .000). A significant effect of session ($F_{2,58}$ = 4.492, p = .041) and a significant task x session interaction ($F_{2,58}$ = 3.558, p = .047) showed an influence of order of measurement in response times. Similar to hit rates this training effect appeared in the high memory condition only ($F_{1,38}$ = 5.915, p = .020) but a trend towards significance in low filtering ($F_{1,38}$ = 3.389, p = .073) and high filtering ($F_{1,38}$ = 3.133, p = .085) condition showed that response times during filtering were not completely unaffected.

Neither a main effect of placebo group ($F_{1,36}$ = .210, p = .649) nor a task x placebo group interaction ($F_{1,36}$ = .377, p = .543) was found in correct rejections thus data were collapsed over both groups. A succeeding rANOVA for the combined groups revealed a main effect of task ($F_{1,38}$ = 44.768, p = .000) but neither a significant effect of session ($F_{1,38}$ = .205, p = .654) nor a task x session interaction ($F_{1,38}$ = .000, p = 1.000). Analysis of response times corresponding to correct rejection rate revealed neither a main effect of placebo group ($F_{1,36}$ = 1.275, p = .266) nor a task x placebo group interaction ($F_{1,36}$ = .086, p = .771) thus data were collapsed over both groups as well. A succeeding rANOVA for the combined groups revealed neither a main effect of task ($F_{1,38}$ = .494, p = .486) nor a significant task x session interaction ($F_{1,38}$ = .000, p = .984) but a significant main effect of session ($F_{1,38}$ = 4.150, p = .049). This effect was driven by a tendency towards a significant difference in response times between sessions (LFLM: $F_{1,38}$ = 3.802, p = .059; HFLM: $F_{1,38}$ = 3.856 p = .057). The distractor in the HFLM condition which had the same color as the target was more often memorized as a target than the distractor, which had a different color than the target (LFLM: 98.14 % ± .38 SEM, p = .000), leading to lower correct rejections (HFLM: 91,72 % ± 1.03 SEM). This difference was not reflected in the corresponding response times (LFLM: 722.70 ms ± 13.43 SEM; HFLM: 717.59 ms ± 13.42 SEM).

A univariate ANOVA of the filter deficit revealed no main effect of placebo group ($F_{1,36}$ = .013, p = .910) thus data were collapsed over both groups. A succeeding ANOVA revealed no significant effect of session ($F_{1,38}$ = .640, p = .429). A univariate ANOVA of the memory deficit revealed no main effect of placebo group ($F_{1,36}$ = 1.373, p = .249) thus data were collapsed over both groups. A succeeding ANOVA revealed a significant main effect of session ($F_{1,38}$ = 4.484, p = .041) that was due to a decrease of memory deficit from the first (13.80 ± 2.06 SEM) to the second session (7.91 ± 1.87 SEM). The mean filter deficit was 3.49 (± 0.81 SEM) and the mean memory deficit was 10.56 (± 1.44 SEM) on average. Higher values indicate a poor filtering and memory performance.

Elderly participants

Means and standard errors are graphed in Fig. 4.2 and can be depicted from Tab. 4.1 including statistical values. Analysis of hit rates by a rANOVA revealed neither a main effect of placebo group ($F_{1,34}$ = .140, p = .711) nor a task x placebo group interaction ($F_{2,68}$ = .945, p = .394) thus data were collapsed over both groups. A succeeding rANOVA for the combined groups revealed a main effect of task ($F_{2,72}$ = 18.142, p = .000) and session ($F_{1,36}$ = 11.176, p = .002) but no significant task x session interaction ($F_{2,72}$ = .380, p = .685). Performance in the NFHM condition (77.94 % ± 21.79 SEM) was significantly lower than the LFLM (86.71 % ± 1.61 SEM, p = .000) and HFLM condition (84.06 % ± 1.77 SEM, p = .001). Performance in filtering conditions did not differ significantly (p = .297). A trainings effect reflected in a significant main effect of session appeared in all conditions: Participants improved performance from the first to the second session in the high memory condition ($F_{1,36}$ = 4.888, p = .034) as well as in the low filtering ($F_{1,36}$ = 9.439, p = .004) and high filtering condition ($F_{1,36}$ = 10.255, p = .003).

Analysis of response times corresponding to hit rates revealed neither a main effect of placebo group ($F_{1,34}$ = .474, p = .496) nor a task x placebo group interaction ($F_{2,72}$ = 1.481, p = .235) thus data were collapsed over both groups. A suc-

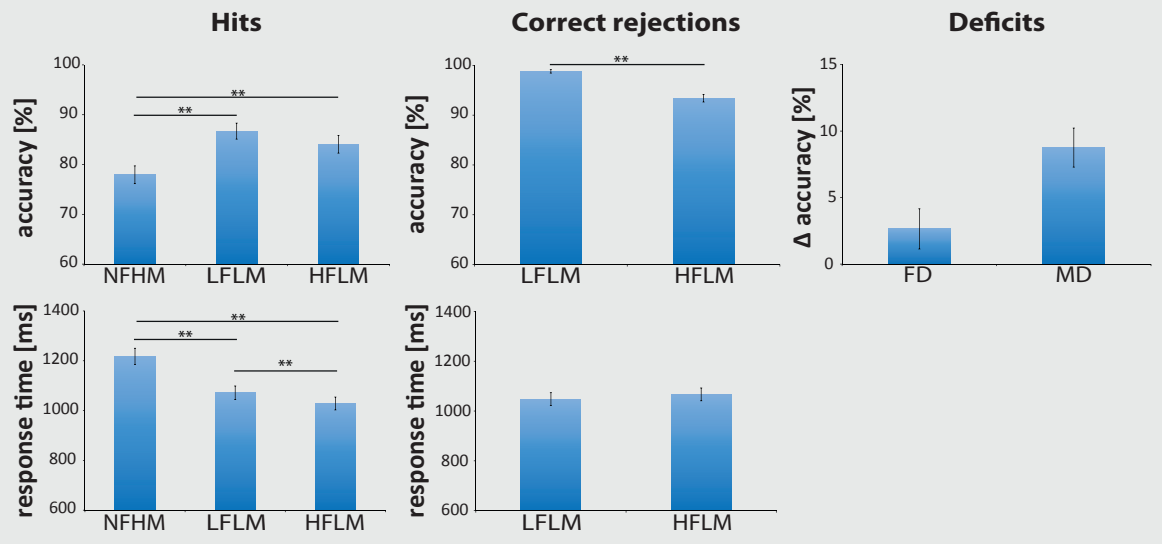

Figure 4.2: Performance of elderly participants in the combined task: *Left column:* Group-averaged hits (%) of all conditions and corresponding response times (ms); *Middle column:* Group-averaged correct rejections (%) of LFLM and HFLM condition referring to lure trials and corresponding response times (ms); *Right column:* Group-averaged filter and memory deficit (Δ%); error bars indicate the standard error of the mean

ceeding rANOVA for the combined groups revealed a significant main effect of task ($F_{2,72}$ = 99.560,p = .000) and session ($F_{1,36}$ = 6.858, p = .013) but no significant task x session interaction ($F_{2,72}$ = .194, p = .824). Participants responded faster in the second session compared to the first across all conditions (NFHM: $F_{1,34}$ = 5.399, p = .026; LFLM: $F_{1,34}$ = 6.924, p = .013; HFLM: $F_{1,34}$ = 6.907, p = .013). The task effect resulted from significantly slower responses in the NFHM condition (1217.64 ± 32.71 SEM) than in the LFLM condition (1071.43 ± 27.36 SEM, p = .000) and in the HFLM condition (1028.45 ± 25.88 SEM, p = .000). Performance in both filtering conditions differed significantly in response time (p = .001).

Analysis of correct rejection rate revealed no significant main effect of placebo group ($F_{1,34}$ = .146, p = .705) but a task x placebo group interaction ($F_{1,34}$ = 5.922, p = .021) thus data were collapsed over both groups and placebo group was included as a between factor in all following analyses. In addition, the ANOVA revealed a significant main effect of task ($F_{1,34}$ = 55.202, p = .000) and a significant task x session interaction ($F_{1,34}$ = 6.017, p = .019) as well as a significant main effect of session ($F_{1,34}$ = 7.731, p = .009). The task effect was due to participants responding

correct in 98.78 % (± .35 SEM) in the LFLM condition and responding less correct in 93.39 % (± .75 SEM) in HFLM condition (p = .000). Post hoc analyses revealed that the effect of session was mainly driven by a trainings effect in the high filtering condition ($F_{1,34}$ = 10.001, p = .003) which was absent in the low filtering condition ($F_{1,34}$ = .484, p = .492). Whereas the strong distractor was correctly responded in 91.38 % (± .95 SEM) in the first session, participants were correct in 95,39 % (± .98 SEM) in the second session.

Analysis of response times corresponding to correct rejection rate revealed neither a main effect of placebo group ($F_{1,34}$ = .232, p = .633) nor a task x placebo group interaction ($F_{1,34}$ = .667, p = .417) thus data were collapsed over both groups. A succeeding rANOVA for the combined groups revealed a trend towards a significant main effect of task ($F_{1,36}$ = 3.754, p = .061) and a significant main effect of session ($F_{1,36}$ = 11.644, p = .002) but no significant task x session interaction ($F_{1,36}$ = .490, p = .489). Response times did not differ between conditions (LFLM: 1047.89 ms ± 25.73 SEM; HFLM: 1066.81 ms ± 25.81 SEM) but between sessions across both conditions (LFLM: $F_{1,36}$ = 12.558, p = .001; HFLM: $F_{1,36}$ = 9.792, p = .004). Whereas participants responded after 1126.94 ms (± 37.65 SEM) in the low filtering and after 1139.02 ms (± 37.57 SEM) in the high filtering condition on the first session, responses were speeded in the second session (LFLM: 968.84 ms ± 23.93 SEM, HFLM: 994.60 ms ± 26.81 SEM).

A univariate ANOVA of the filter deficit revealed no main effect of placebo group ($F_{1,34}$ = 1.537, p = .224) thus data were collapsed over both groups. Session had no significant effect on filter deficit ($F_{1,34}$ = .159, p = .693) which was revealed by a succeeding ANOVA. A univariate ANOVA of the memory deficit revealed no significant main effect of placebo group ($F_{1,34}$ = .022, p = .882) thus data were collapsed over both placebo groups. Session had no significant effect on memory deficit ($F_{1,34}$ = .217, p = .644). The filter deficit was 2.65 (± 1.51 SEM) and the memory deficit was 8.76 (± 1.47 SEM) on average.

Table 4.1: Means and SEM of performance for different response types in the combined task for the group of young and elderly participants; F- and p-values indicate main effects (ME) of age and age x task interaction effects (IE)

			Young	Elderly	ME Age		IE Age x Task	
		Condition	Mean (SEM)	Mean (SEM)	F-value (1,74)	p-value	F-value (2,148)	p-value
Hits	%	NFHM	80.86 (1.41)	77.94 (1.79)	5.984	**.017**	.647	.525
		LFLM	91.42 (.74)	86.71 (1.61)				
		HFLM	87.93 (.99)	84.06 (1.77)				
	ms	NFHM	853.70 (18.82)	1217.64 (32.71)	127.605	**.000**	8.936[1]	**.001**
		LFLM	740.19 (15.13)	1071.43 (27.36)				
		HFLM	732.09 (14.28)	1028.45 (25.88)				
					F-value (1,74)	p-value	F-value (1,74)	p-value
Correct rejections	%	LFLM	98.14 (.38)	98.79 (.35)	2.107[2]	.151	.656[2]	.421
		HFLM	91.71 (1.03)	93.39 (.75)				
	ms	LFLM	722.70 (13.43)	1047.89 (25.73)	181.719	**.000**	4.000	**.049**
		HFLM	717.59 (13.42)	1066.81 (25.81)				
Filter deficit	Δ%		3.41 (.81)	2.65 (1.51)	.216	.643		
Memory deficit	Δ%		10.56 (1.44)	8.76 (1.47)	1.059	.307		

[1] = F(2,127)
[2] = F(1,70)

Comparison between young and elderly participants

A rANOVA with the within factor task, the between factors age (young/elderly) and session (first/second) was carried out to assess whether memory and filtering performance was influenced by age. A significant main effect of age could be observed in hit rates ($F_{1,74} = 5.984$, $p = .017$) and response times ($F_{1,74} = 127.605$, $p = .000$). A task x age interaction did not reach significance in hit rates ($F_{2,\,148} = .647$, $p = .525$) but in response times ($F_{2,122} = 8.936$, $p = .001$). To find out between which conditions these age effects exactly occurred a multivariate ANOVA was calculated for hit rates and response times. This analysis revealed a significantly better performance in young participants than in elderly in both distractor conditions LFLM ($F_{1,\,74} = 8.806$, $p = .004$) and HFLM ($F_{1,\,74} = 4.585$, $p = .036$) but not in the pure memory condition ($F_{1,74} = 1.487$, $p = .227$). Significant age differences were reflected in higher response times in elder in comparison to young participants in all conditions: NFHM ($F_{1,74} = 106.966$, $p = .000$), LFLM ($F_{1,74} = 131.787$, $p = .000$) and HFLM ($F_{1,74} = 117.808$, $p = .000$, Fig. 4.3).

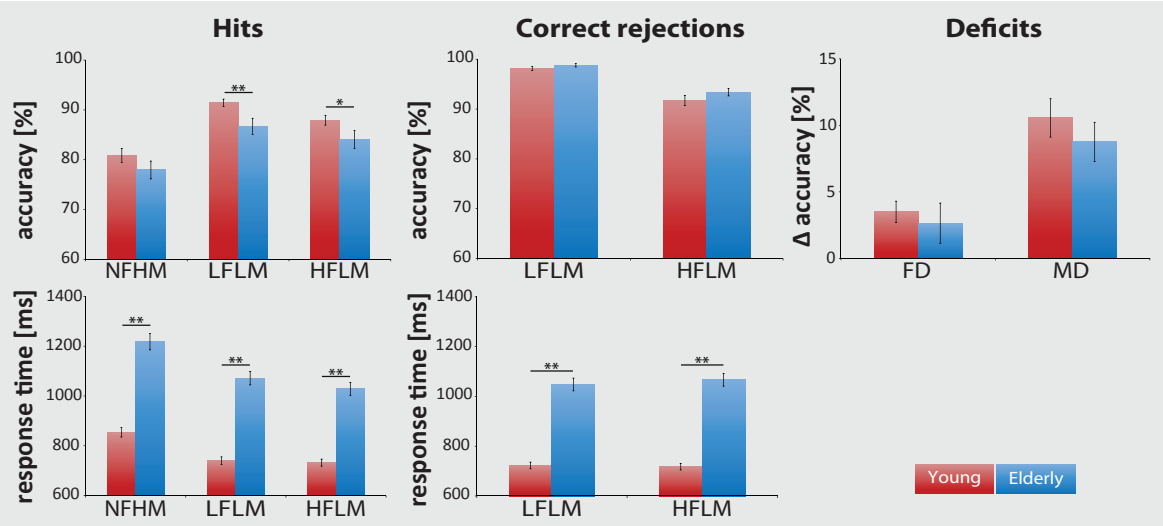

Figure 4.3: Comparison of performance of young (red) and elderly (blue) participants in the combined task: *Left column:* Group-averaged hits (%) of all conditions and corresponding response times (ms); *Middle column:* Group-averaged correct rejections (%) of LFLM and HFLM condition referring to lure trials and corresponding response times (ms); *Right column:* Group-averaged filter and memory deficit (Δ%); error bars indicate the standard error of the mean

Because of a significant effect of placebo group in the correct rejections of elderly participants, the between factor "placebo group" was included in the following ANOVA. Age showed neither a significant main effect in the correct rejections ($F_{1,70} = 2.107$, $p = .151$) nor a significant task x age interaction ($F_{1,70} = .656$, $p = .421$). In contrast, a significant main effect of age was found in corresponding response times ($F_{1,74} = 181.719$, $p = .000$) as well as a significant task x age interaction ($F_{1,74} = 4.000$, $p = .049$). The effects of slower response times in elderly when the distractor was probed were found in LFLM ($F_{1,74} = 163.462$, $p = .000$) and HFLM ($F_{1,74} = 179.946$ $p = .000$) condition following the results of a succeeding multivariate ANOVA.

The results of a univariate ANOVA that was carried out on filter deficit with regard to age was not found to be significant ($F_{1,74} = .216$, $p = .643$) as well as the effect of age on memory deficit ($F_{1,74} = 1.059$, $p = .307$). See Fig. 4.3 and Tab. 4.1 for means and standard errors.

4.1.2 *Functional MRI-data:* Combined task

Young participants

A rANOVA with the within factor task (NFHM/LFLM/HFLM) and the between factor placebo group (dopamine/galantamine placebo group) revealed no significant main effect of placebo group at a threshold level of FDR = .05 so placebo data were collapsed over both groups. A succeeding ANOVA revealed no significant effect of session at a threshold level of FDR = .05. Clusters of significant memory dependent

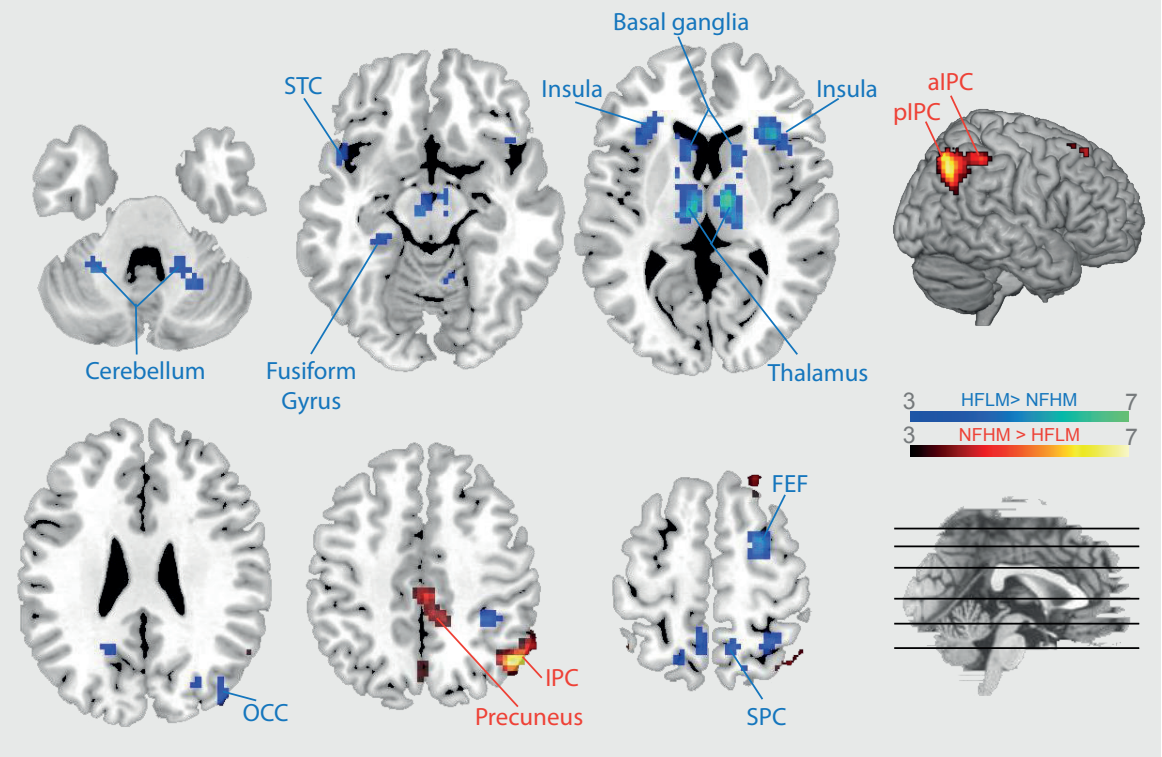

Figure 4.4: Task-related changes in BOLD signal during encoding in young participants: The color bar indicates the T-value; red/yellow: group activation map for the contrast NFHM > HFLM; blue/green: group activation map for the contrast HFLM > NFHM; FDR = .05 (aIPC/pIPC = anterior/posterior inferior parietal cortex, FEF = frontal eye fields, STC = superior temporal cortex, OCC = occipital cortex, V3 = visual area 3, SPC = superior parietal cortex)

activation were identified in the right inferior parietal Cortex (IPC) with a peak in anterior (aIPC) and posterior (pIPC) parts of the IPC and in the right precuneus (Fig. 4.4) via an effect-of-interest t-test (NFHM > HFLM).

In order to address a net of co-activated brain regions during attentional filtering we looked which areas were more active during the condition with high filtering demands

(HFLM) than during the condition in which no filtering was required (NFHM). This contrast revealed the bilateral thalami, basal ganglia, insulae and cerebellum at a significance level of $p > .05$ (FDR corrected). In addition, we found task-related activation in the right superior parietal cortex (SPC), FEF, visual area 3 (V3) in OCC, left superior temporal cortex (STC) and the fusiform gyrus. MNI-Coordinates of cluster peaks are reported in Tab. 4.2. For further analysis of all regions of interest spherical ROIs were centered on each cluster peak.

Table 4.2: Peak activations of clusters for the memory and filter contrast of young participants

Anatomical structure	Hemisphere	Clustersize	Max. T-value	MNI coordinates (x,y,z)		
			NFHM > HFLM			
pIPC	R	178	6.54	45	-67	40
aIPC	R		4.86	54	-43	49
Precuneus	R	47	4.73	9	-37	34
			HFLM > LFHM			
Thalamus	R	224	6.71	9	-16	10
	R		5.22	12	-16	-8
Basal Ganglia (Striatum/Putamen)	R		4.82	15	8	-8
Thalamus	L	112	6.19	-12	-19	7
	L		3.97	-15	-1	-5
Basal Ganglia (Striatum/Caudate Ncl.)	L	18	4.24	-12	11	4
Basal Ganglia (Pallidum)	L	12	4.09	-18	-1	4
Insula	R	120	5.67	33	20	4
	L	22	4.25	-33	26	4
FEF	R	63	4.89	24	-1	55
STC	L	14	3.82	-51	8	-17
SPC	R	23	4.14	33	-43	43
	R	22	4.02	27	-55	52
	R	12	4.00	9	-58	58
OCC (V3)	R	15	4.00	24	-73	28
Fusiform G.	L	10	3.75	-27	-34	-17
Cerebellum	R	22	4.07	12	-52	-26
	L	24	4.57	-33	-58	-32

Note: L = left, R = right

Young Participants: ROI Analysis

A rANOVA of beta values extracted from each ROI of the memory contrast was carried out with the within subject factor region (aIPC, pIPC, precuneus) and the within subject factor task (NFHM, LFLM, HFLM). A main effect of region ($F_{2,78} = 9.040$, $p = .000$) as well as a main effect of task ($F_{2,\ 78} = 26.099$, $p = .000$) and a region x task

interaction ($F_{4,\ 156}$ = 2.600, p = .038) was found to be significant. For a refined analysis data of each ROI were separately subjected to a rANOVA with the within subject factor task (NFHM, LFLM, HFLM). Because of the contrast, ß-values were of course higher in the NFHM condition than in the HFLM condition but the whole pattern differed between regions (Fig. 4.5). A similar activation pattern emerged

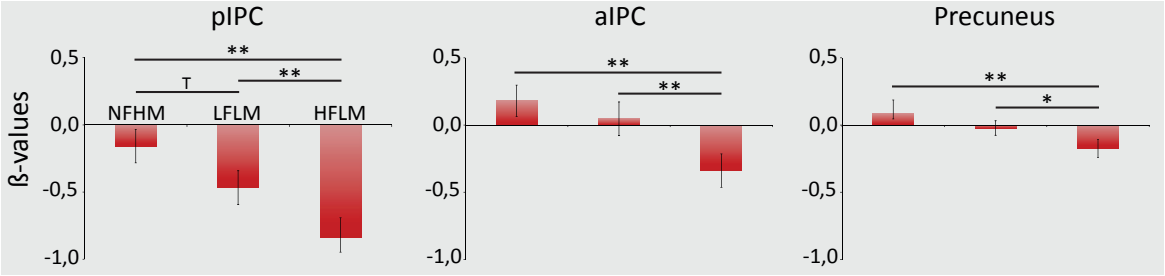

Figure 4.5: Mean ß-values of young participants from ROIs of memory contrast separately depicted for each condition in both rIPC regions and precuneus

in the aIPC and precuneus with positive beta values in the high memory condition (NFHM), negative values in the low memory condition with strong distractors (HFLM) and beta values of low load condition in between. In contrast, all beta values in the pIPC were negative with increasing beta values from high filtering demands (HFLM) over low filtering demands (LFLM) to no filtering demands (NFHM). These patterns were reflected in significant main effects of task in the pIPC ($F_{2,78}$ = 15.269, p = .000), aIPC ($F_{2,78}$ = 10.916, p = .000) and precuneus ($F_{2,78}$ = 8.216, p = .001) following a rANOVA for each region separately (Tab. A.2).

An additional rANOVA was carried out for the beta values of ROIs of the filter contrast with the within subject factors region (thalamus, basal ganglia etc.) and task (NFHM, LFLM, HFLM). The rANOVA yielded a main effect of region ($F_{5,195}$ = 67.959, p = .000), a main effect of task ($F_{2,78}$ = 38.163, p = .000) as well as a task x region interaction ($F_{34,477}$ = 3.958, p = .000). For further analysis beta values of each region were subjected to a rANOVA with the within subject factor task separately. For all regions significant task effects were found (all p-values $<$ .05, Tab. A.2). A pattern of beta values increasing significantly from no filtering over low filtering to high filtering condition was found in the bilateral thalami (Fig. 4.6). In contrast, no filtering and

low filtering condition in the bilateral insulae did not differ but were significantly lower than beta values in the high filtering condition. Higher beta values in both filtering conditions in contrast to the high memory conditions were found in the basal ganglia, right FEF, right SPC, right OCC (V3) and left fusiform gyrus. Beta values in the high memory and high filtering condition did differ in the left STC and bilateral cerebellum but did not differ from low filtering (low memory) condition.

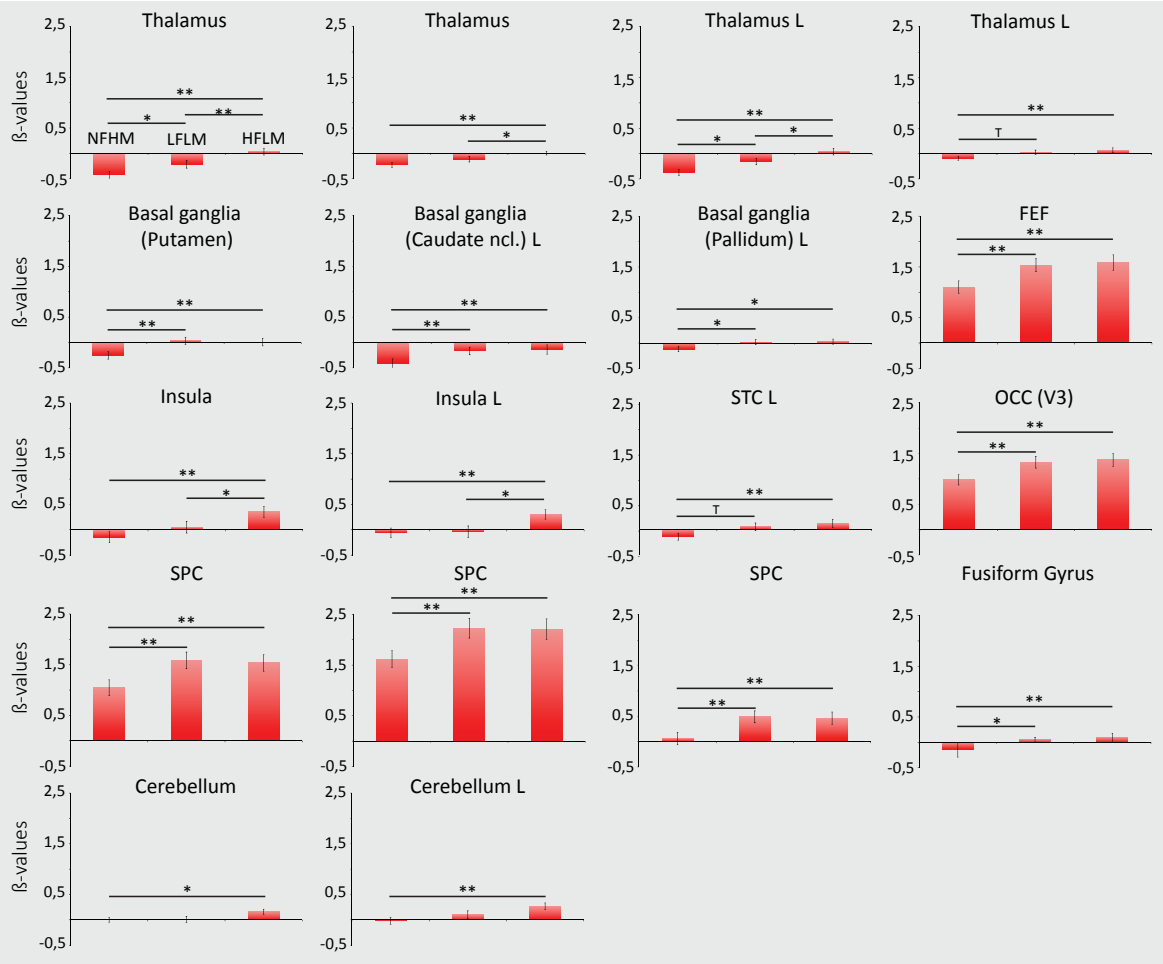

Figure 4.6: Mean ß-values of young participants from ROIs of filter contrast separately depicted for each condition

Elderly participants

A rANOVA revealed no effects of placebo group at a threshold level of FDR = .05 so subsequent rANOVAs were carried out with the within factor task and the between

factor session. No effect of session at a threshold level of FDR = .05 was found following this rANOVA. Stronger activation related to the pure memory condition (NFHM) in comparison to the distractor condition (HFLM) was found in anterior and posterior parts of the bilateral IPC, in right posterior and left STC, right pTC, right parahippocampal cortex (PHC) and cingulate gyrus (Fig. 4.7).

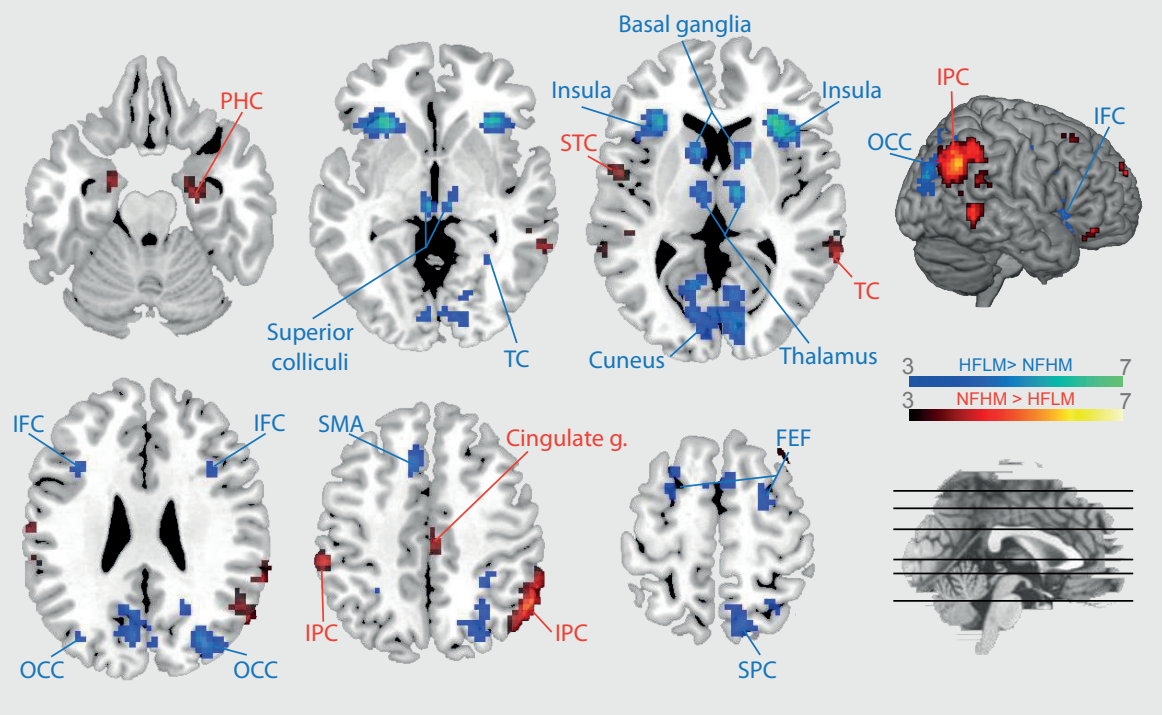

Figure 4.7: Task-related changes in BOLD signal during encoding in elderly participants: The color bar indicates the T-value; red/yellow: group activation map for the contrast NFHM > HFLM; blue/green: group activation map for the contrast HFLM > NFHM, FDR = .05 (pIPC = posterior inferior parietal cortex, aIPC = anterior inferior parietal cortex, pTC = posterior temporal cortex, STC = superior temporal cortex, PHC = parahippocampal cortex, IFG = inferior frontal gyrus, SMA = supplementary motor area, FEF = frontal eye fields, OCC = occipital cortex, SPC = superior parietal cortex)

The filter contrast revealed co-activation of the bilateral thalami, bilateral basal ganglia (striatum/caudate ncl.), bilateral superior colliculi, parts of left lateral geniculate body, bilateral insulae, bilateral IFG, left SMA, bilateral FEF, right pTC, left SPC, bilateral OCC with IPC and SPC and bilateral Cuneus. MNI-Coordinates of cluster peaks are reported in Tab. 4.3. Because a huge cluster was found covering tiny structures like the thalami and the basal ganglia all peaks of this cluster with a minimum distance of 4 mm were separately analyzed. This clusters included the bilateral tha-

lami and the bilateral basal ganglia (caudate nucleus and substantia nigra) as well as the bilateral superior colliculus. See Tab. 4.3 for MNI-Coordinates of cluster peaks. For further analysis of all regions of interest spheric ROIs were centered on each cluster peak.

Table 4.3: Peak activations of clusters for the memory and filter contrast of elderly participants

Anatomical Structure	Hemisphere	Cluster size	Max. T-Value	MNI coordinates (x,y,z)		
			NFHM>HFLM			
pIPC	R	202	5.69	54	-61	34
aIPC	L	16	4.24	-57	-37	40
aIPC	L	16	4.12	-66	-19	25
pTC	R	37	4.78	63	-49	1
STC	L	10	4.21	-57	-1	1
PHC	R	13	4.02	24	-16	-26
Cingulate Gyrus	-	13	3.97	0	-28	37
			HFLM>NFHM			
Thalamus	R	350	6,44	9	-16	7
Superior Colliculus	L		5,78	-6	-28	-5
Basal ganglia (Striatum/Caudate Ncl.)	L		5,14	-12	8	4
Basal ganglia (Striatum/Caudate Ncl.)	R	72	5,43	12	5	1
Lateral geniculate body	L	10	3,87	-24	-22	-2
Insula	R	237	7,73	30	26	-2
	L	243	6,60	-33	23	-2
IFG	R	48	4,50	36	14	25
	L	50	4,42	-39	14	25
SMA	L	191	4,72	-9	14	46
FEF	R	99	4,04	33	-4	49
	R		3,39	24	-1	70
	L	66	3,74	-27	2	55
pTC	R	23	3,60	42	-52	-14
SPC	L	20	3,59	-30	-55	49
OCC	R	49	3,62	33	-61	-14
OCC/IPC/SPC	R	531	5,66	30	-82	25
	R		4,36	12	-73	49
	L		3,96	-12	-58	52
OCC	L	33	3,60	-39	-79	25
Cuneus	R	749	5,69	3	-82	-2
	L		5,41	-9	-76	16
	R	24	3,93	18	-58	19
			Peak activatio of Thalamus Cluster from HFLM>NFHM			
Thalamus	R	350	6,44	9	-16	7
Superior Colliculus	L		5,78	-6	-28	-5
Basal ganglia (Striatum/Caudate Ncl.)	L		5,14	-12	8	4
Superior Colliculus	R		5,13	6	-25	-5
Thalamus	L		5,03	-15	-13	10
Basal ganglia (Striatum/Caudate Ncl.)	L		4,18	-18	-1	16
Thalamus	R		3,51	9	-16	-5

Note: L = left, R = right

Elderly Participants: ROI Analysis

Beta Values of ROIs from the memory contrast were subjected to a rANOVA with the within subject factor region (IPC, pTC, STC, PHC, cingulate gyrus) and the within subject factor task (NFHM, LFLM, HFLM). This analysis revealed a main effect of region ($F_{(4,163)} = 7.752$, $p = .000$) and task ($F_{(2,61)} = 26.588$, $p = .000$) as well as a task x region interaction ($F_{(7,263)} = 2.779$, $p = .008$). For a more detailed analysis a rANOVA was carried out for each ROI separately with the within subject factor task (NFHM, LFLM, HFLM). F- and p-values can be depicted from Tab. A.3, averaged means are graphed in Fig. 4.8.

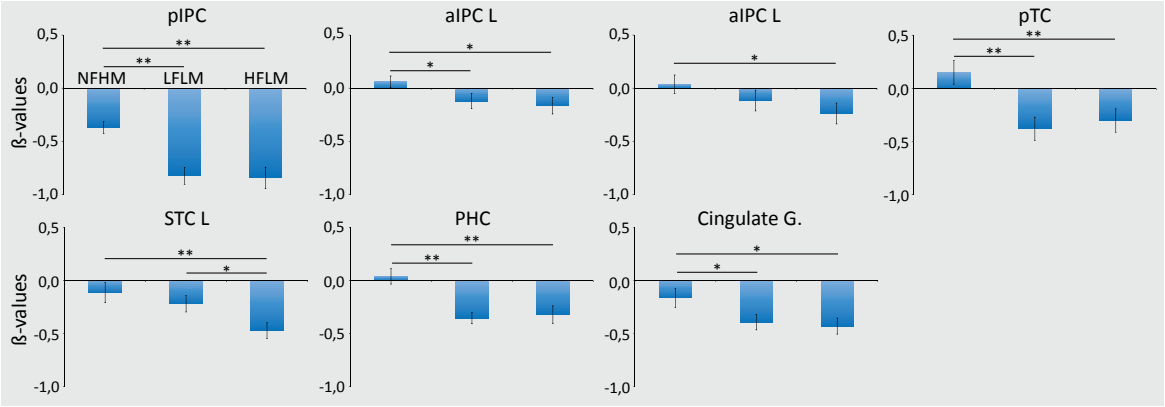

Figure 4.8: Mean ß-values of elderly participants from ROIs of memory contrast separately depicted for each condition

In the anterior part of the left IPC cluster only beta values for the NFHM and HFLM condition differed significantly. In contrast, in the left STC the high filtering condition was significantly higher than the no and low filtering conditions. All other areas showed the same activation pattern with beta values the high memory condition being significantly higher than beta values of both filtering conditions.

A rANOVA, including all filtering regions with the within subject factor region and the within subject factor task (NFHM/LFLM/HFLM), revealed a main effect of task ($F_{2,74} = 42.236$, $p = .000$), a main effect of region ($F_{11,420} = 38.489$, $p = .000$) and a task x region interaction ($F_{52,1924} = 3.463$, $p = .000$). Separate rANOVAs for each region with the within subject factor task revealed main effects in all regions (all p-values $< .05$, Tab. A.3). A significant increase in beta values from no filtering

demands over low filtering demands to high filtering demands were observed in the right thalamus and SMA (Fig. 4.9).

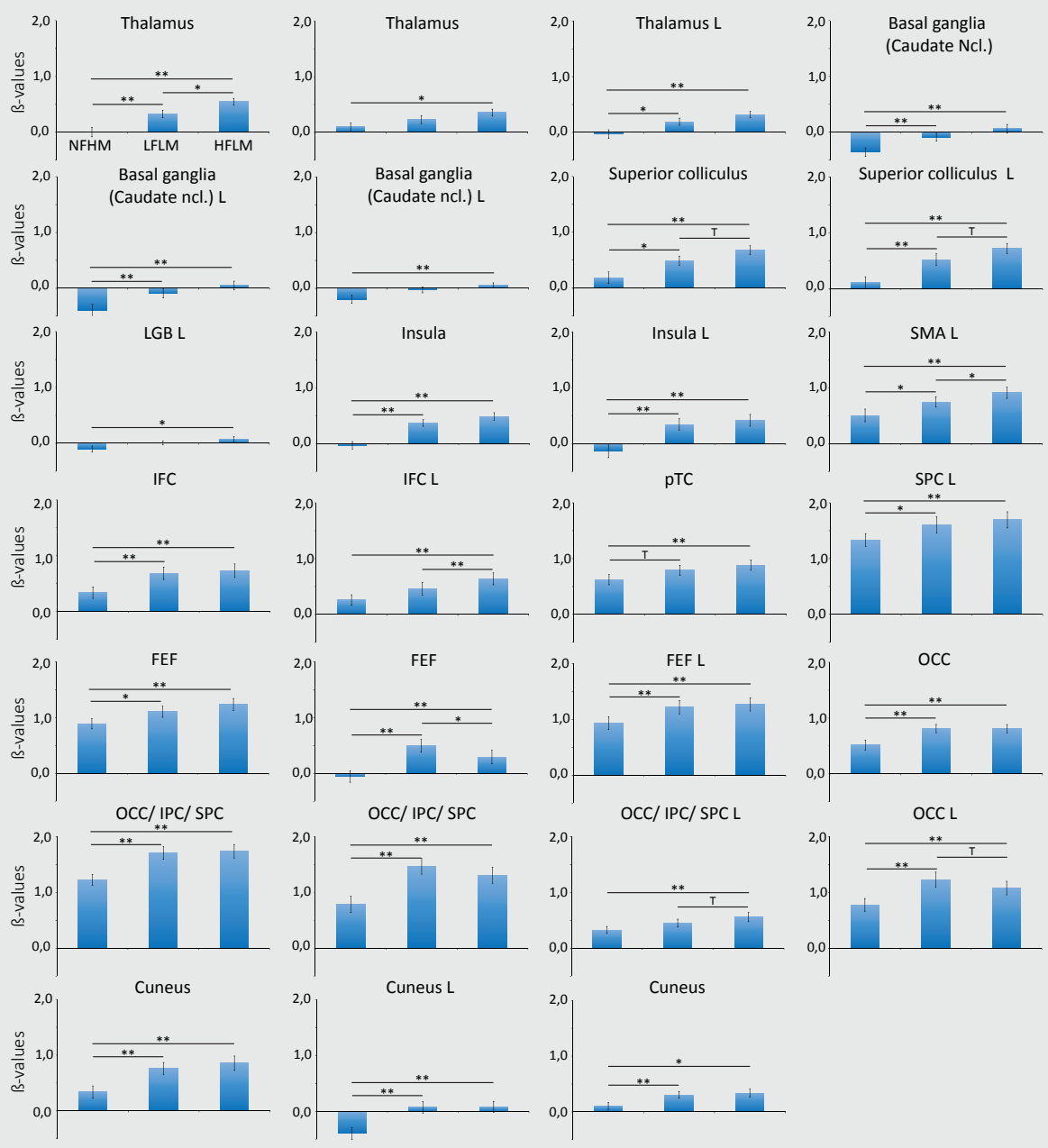

Figure 4.9: Mean ß-values of elderly participants from ROIs of filter contrast separately depicted for each condition

Significant differences between the pure memory condition and the high filtering condition were found in the lateral geniculate body, left caudate nucleus and right pTC. In the left IFG beta values in the high filtering condition were significantly higher

than in the no filtering and low filtering condition. In all other brain regions the same pattern emerged: no differences were found between both filtering conditions but beta values were significantly higher than in the no filtering condition.

Comparison between young and elderly participants

In both age cohorts the right IPC was found to be active during storage (Fig. 4.10). Whereas young participants recruited the precuneus in addition, left IPC, right pTC, left STC, right PHC and cingulate gyrus were activated more in the elderly cohort. During filtering common activations were found in the bilateral thalami, bilateral

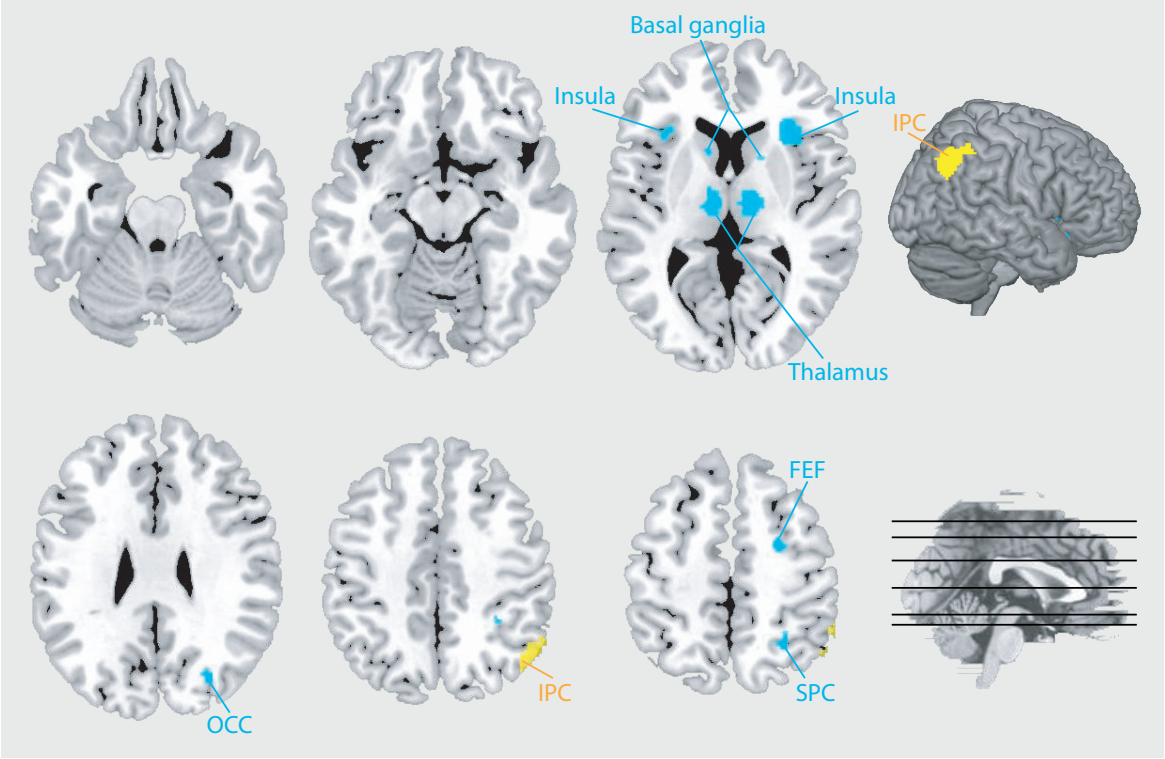

Figure 4.10: Commonly task-related changes in BOLD signal in the group of young and elderly participants during the memory (yellow) and filter contrast (blue)

insulae, bilateral basal ganglia, right FEF, right SPC as well as right OCC (V3). Additionally to these brain regions the right cerebellum and PHC were also active during filtering in the cohort of young participants. The elderly recruited more brain regions in addition to the previously mentioned regions: The filter contrast revealed the left lateral geniculate body, bilateral IFG, left SMA, right pTC and cuneus. OCC

and FEF that were found lateralized to the right hemisphere in young participants were spread over both hemispheres in the cohort of elderly.

4.1.3 Interaction of behavioral performance and storage related BOLD activity

Because hypotheses were mainly based on the association between filter performance and storage related hemodynamic response, associations between filter activity and behavioral performance was not reported here.

Young participants

Hits in the LFLM condition were significantly associated with effective storage activity in the right pIPC (r = -.398, p = .012, Fig. 4.11). In addition, effective storage ac-

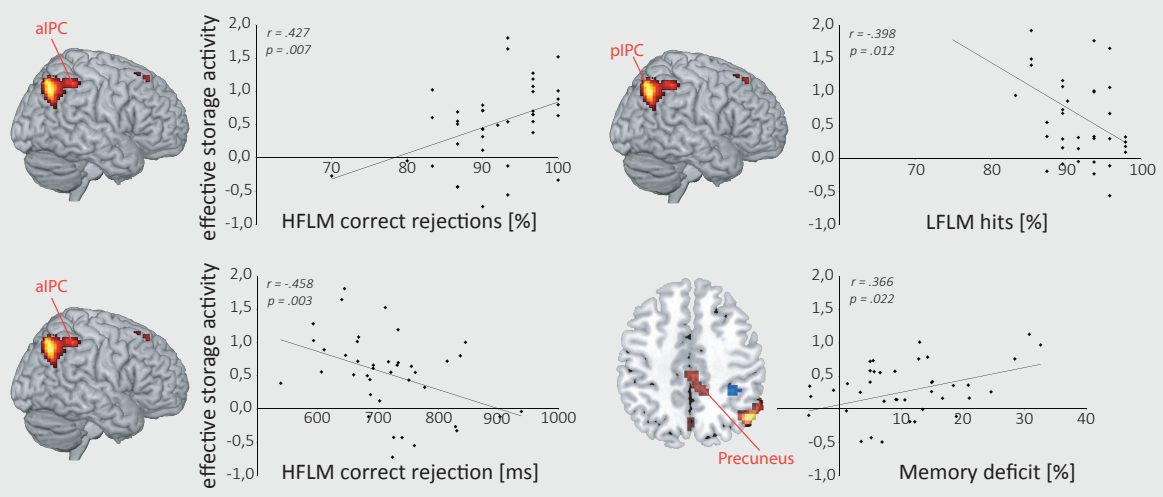

Figure 4.11: *Left column:* Correlation of effective storage activity in aIPC with correct rejections (%) and corresponding response times (ms) in the HFLM condition in young; *Right upper column:* Correlation of effective storage activity in pIPC with hits (%) in LFLM condition; *Right lower column:* Correlation of individual BOLD signal change differences in precuneus with memory deficit (Δ%)

tivity in the anterior region of IPC was significantly correlated with correct rejections (r = .427, p = .007) and corresponding response times (r = -.458, p = .003) in the high filtering condition. Participants with greater activity difference between the high memory (no filtering) and low memory (high filtering) condition were more accurate and faster in rejecting the distractor as a target. Activation in the precuneus was

significantly positive correlated with the memory deficit (r = .366, p = .022). Participants with increased effective storage activity in the precuneus showed a poor memory performance reflected in an increased memory deficit. All correlation coefficients and p-values can be depicted from Tab. A.4.

Elderly participants

Higher accuracy and faster responses during the correct rejection of the strong distractor were associated with decreased effective storage activity in one part of the left aIPC (p correct: r = .428, p = .013, RT: r = -.363, p = .035) and with response times only in the other part of the left aIPC (r = -.428, p = .032, Fig. 4.12). No further significant correlations were found between behavioral performance and effective storage activity in the elderly cohort. All correlation coefficients and p-values can be depicted from Tab. A.5.

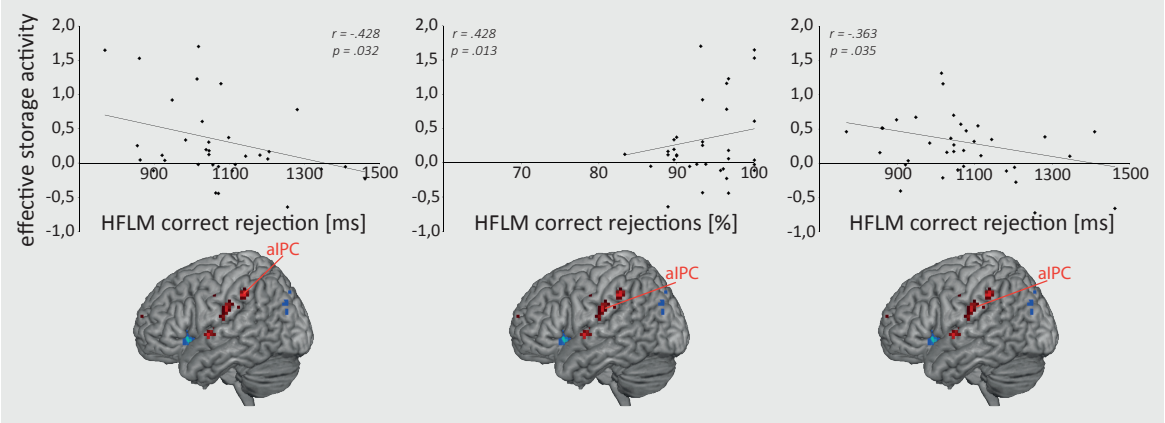

Figure 4.12: Correlation of effective storage activity in in aIPC with correct rejections (%) and corresponding response times (ms) in the HFLM condition in elderly

Comparison between young and elderly participants

Whereas impairments in filtering performance were correlated with changes in hemodynamic response related to memory storage in anterior parts of the right IPC in young participants this relation was seen in the elderly in anterior parts of the left IPC. Moreover, a correlation between memory deficit and precuneus activity was observed in the young cohort only.

4.1.4 *Structural MRI-data:* Substantia nigra and basal forebrain

Young participants: SN_{MT} and SN_{vol}

A ANOVA with the between subject factor placebo group revealed no significant effect of placebo group on SN_{MT} ($F_{1,36} = 1.575$, $p = .218$) or SN_{vol} ($F_{1,36} = 1.325$, $p = .257$) thus data were collapsed over both placebo groups for further analysis. The order of measurement had no effect on SN_{MT} ($F_{1,36} = .674$, $p = .417$) or SN_{vol} ($F_{1,36} = 2.207$, $p = .146$). Means and standard errors can be depicted from Tab. 4.4.

Table 4.4: Means and SEM of SN_{MT}, SN_{vol} and BF_{vol}

		Young Mean (SEM)	Elderly Mean (SEM)
Substantia nigra	MTRatio	.17 (.00)	.39 (.00)
	Volume [10^3 mm^3]	.38 (.01)	.24 (.01)
Basal forebrain	Volume [10^3 mm^3]	.34 (.01)	.26 (.01)

Young participants: BF_{vol}

A ANOVA that was carried out for BF_{vol} revealed a significant main effect of placebo group ($F_{1,36} = 13.678$, $p = .000$) but no effect of session ($F_{1,36} = .005$, $p = .944$)

Elderly participants: SN_{MT} and SN_{vol}

Placebo groups differed significantly in SN_{vol} ($F_{1,32} = 28.525$, $p = .000$) but not in SN_{MT} ($F_{1,32} = .249$, $p = .621$). The order of measurement had no effects on SN_{vol} ($F_{1,32} = .144$, $p = .707$) or SN_{MT} ($F_{1,32} = .519$, $p = .476$).

Elderly participants: BF_{vol}

A ANOVA revealed no significant difference between placebo groups in terms of BF_{vol} ($F_{1,34} = 1.567$, $p = .219$) so data were collapsed over both groups for further analysis. Moreover, BF_{vol} was not influenced by the order of measurement ($F_{1,34} = .038$, $p = .846$).

Comparison between young and elderly participants: SN_{MT}, SN_{vol} and BF_{vol}

Because of the use of different MR scanner for both age cohorts, SN_{MT}, SN_{vol} and BF_{vol} were not compared between age groups.

4.1.5 Effects of structural integrity on performance in combined task

Because of significant differences between placebo groups in BF_{vol} of the young participants and SN_{vol} of the elderly participants, "placebo group" was included as a covariate to all correlation analyses.

Young participants: Effects of SN_{MT} and SN_{vol}

Partial correlations revealed no significant correlations between hit rates, correct rejections or filter and memory deficit and SN_{MT} or SN_{vol} (all p-values $> .05$) except a significant correlation between SN_{vol} and memory deficit ($r = -.334$, $p = .040$, Fig. 4.13). A greater substantia nigra was accompanied by a smaller memory deficit. All correlation coefficients and p-values can be depicted from Tab. A.6.

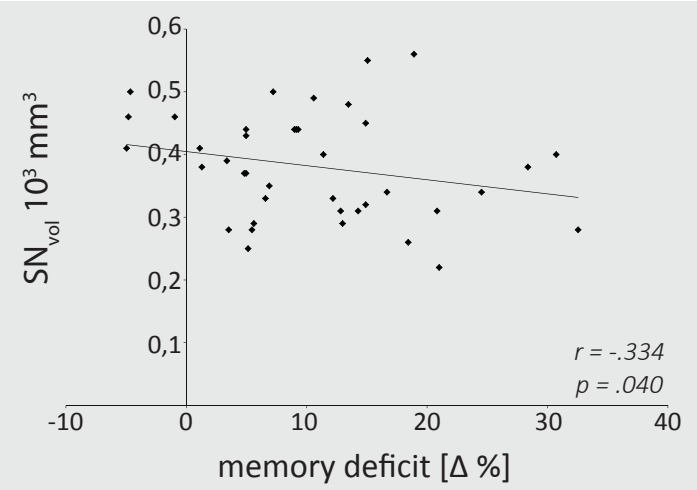

Figure 4.13: Correlation of individual memory deficit (Δ%) with SN_{vol} in young

Young participants: Effects of BF_{vol}

No significant correlations were found between hit rates, correct rejections or filter and memory deficit and BF_{vol} in the placebo group (all p-values $> .05$). All correlation coefficients and p-values can be depicted from Tab. A.6.

Elderly participants: Effects of SN_{MT} and SN_{vol}

Partial correlations revealed no significant correlations between behavioral data and SN_{vol} or SN_{MT} (all p-values $> .05$) except a significant association between SN_{MT} and accuracy in the correct rejection of the weak distractor (r = -.387, p = .028) as well as accuracy in the hits of the LFLM condition (r = -.450, p = .010, Fig. 4.14).

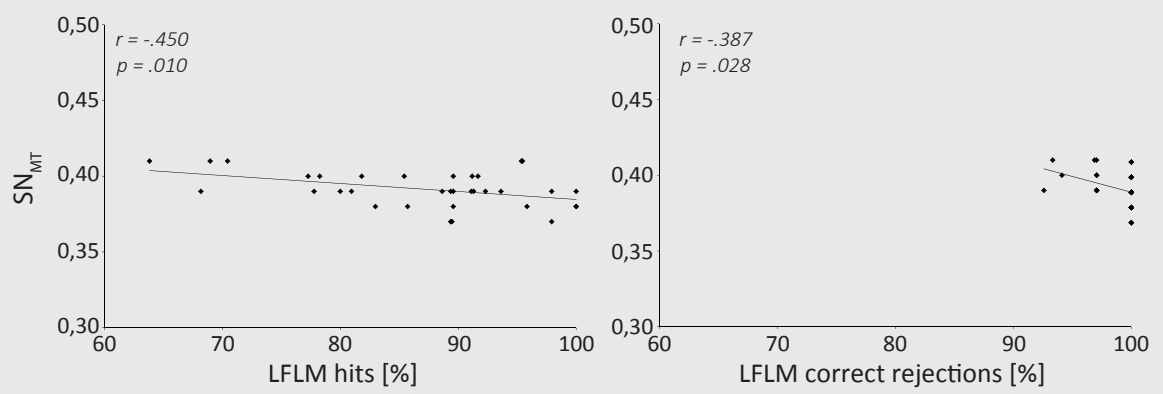

Figure 4.14: *Left column:* Correlation of hits (%) in LFLM condition with SN_{MT} in elderly; *Right column:* Correlation of correct rejections (%) of LFLM condition with SN_{MT} in elderly

Elderly participants: Effects of BF_{vol}

No significant correlations were found between behavioral parameters and BF_{vol}. All correlation coefficients and p-values can be depicted from Tab. A.6.

Comparison between young and elderly participants: SN_{MT}, SN_{vol} and BF_{vol}

Whereas a relation between SN_{vol} and memory deficit was found in the young, SN_{MT} in the elderly was related to performance in correct rejections and hits of the LFLM condition. No significant correlations between behavioral measures and BF_{vol} were found in any of the age cohorts.

4.2 Influence of working memory capacity on memory and filter correlates

4.2.1 *Behavioral data:* Working memory capacity

Young participants

A rANOVA revealed neither a significant main effect of placebo group ($F_{1,38} = 1.701$, $p = .200$) nor a set size x placebo group interaction ($F_{3,\ 99} = .586$, $p = 602$) thus data were collapsed over both placebo groups. A succeeding rANOVA revealed a significant main effect of set size ($F_{3,\ 102} = 51.961$, $p = .000$). Participants increased VWM capacity with increasing set size from two to three ($p = .000$) and from four to five ($p = .000$) presented items (Fig. 4.15). As an index of VWM capacity the capacity for a set size of two, three and four were averaged for each participant, leading to a mean VWM capacity of 2.19 (.05 SEM) for the group of young participants.

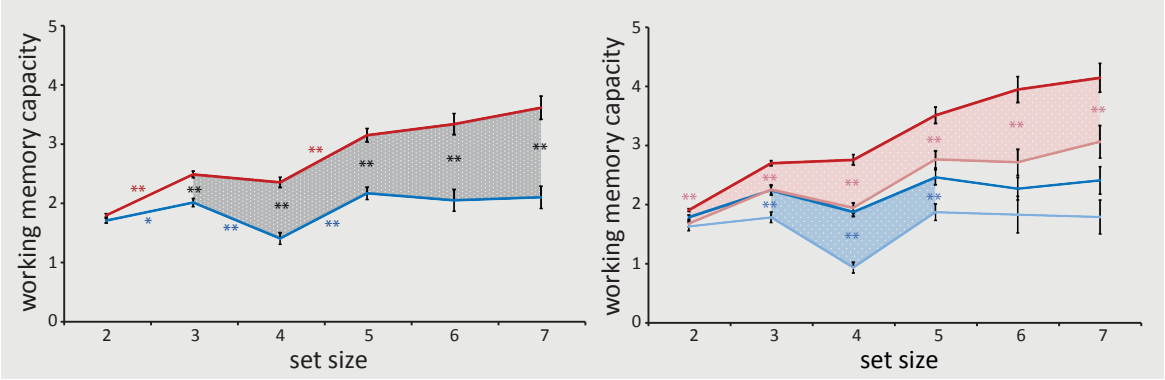

Figure 4.15: *Left column:* Group-averaged VWM capacity for young (red) and elderly (blue) participants; *Right column:* Group-averaged VWM capacity for young (red) and elderly (blue) participants of low (bright) and high (dark) performance groups

Elderly participants

A rANOVA revealed a significant main effect of placebo group ($F_{1,36} = 3.248$, $p = .044$) and a set size x placebo group interaction ($F_{3,\ 106} = 4.171$, $p = .007$) thus data were collapsed over both placebo groups and "placebo group" was included as a between factor for further analyses. A significant main effect of set size was found in addition

($F_{3,106}$ = 8.802, p = .000). A similar pattern as in the young participants emerged in the elderly (Fig. 4.2). Elder participants showed a significant increase in VWM capacity from two to three (p = .001) and from four to five items (p = .000) but a significant drop from three to four items (p = .000). The averaged WMC for the set size of two, three and four was 1.69 (.05 SEM).

Comparison between young and elderly participants

A rANOVA with the between subject factor age was calculated to prospect age effects. Beneath a main effect of set size ($F_{3,\ 224}$ = 45.001, p = .000) and age ($F_{1,76}$ = 52.933, p = .000) a set size x age effect emerged ($F_{3,224}$ = 12.998, p = .000), pointing to age dependent changes in the WMC (Fig. 4.15). A succeeding multivariate ANOVA was carried out to find out during which set sizes performance was influenced by age. Young participants outperformed the elderly in all set sizes from three to seven (all p-values = .000, Tab. 4.5). When only two rectangles had to be memorized VWM capacity was independent of age (p = .113). The average VWM capacity for a set size of two to four items was significantly higher in the younger participants than in the elderly ($F_{1,76}$ = 47.444, p = .000).

Table 4.5: Mean VWM capacity for each set size in the working memory capacity task for the young and elderly participants and age differences indicated by F- and p-values (df = 153)

Set size	Young (SEM)	Elderly (SEM)	F-Value (1,76)	p-Value
2	1.78 (.03)	1.69 (.04)	2.573	.113
3	2.47 (.06)	1.99 (.07)	31.592	**.000**
4	2.33 (.09)	1.39 (.10)	49.499	**.000**
5	3.13 (.11)	2.15 (.10)	39.933	**.000**
6	3.31 (.18)	2.03 (.18)	28.043	**.000**
7	3.59 (.20)	2.08 (.19)	28.766	**.000**
mean WMC (2-4)	2.19 (.05)	1.69 (.05)	45.444	**.000**

A refined analysis was carried out to find out whether elder participants with a high performance were as good as young participants with a poor performance. For that purpose both age cohorts were separated into two groups each based on the VWM capacity median which was 1.70 for the elderly and 2.18 for the young participants. The separation of groups by median split is a common procedure in VWM capacity

research and is described in several studies (e.g. Vogel *et al.*, 2005), A comparison of performances in all groups was carried out via a rANOVA with the within subject factor set size (two to seven) and the between subject factors performance group (Young: low/high VWM capacity; Elderly: low/high VWM capacity) and placebo group. In case of significant main effects, comparative analyses of the group data were performed using a subsequent univariate ANOVA, that was carried out to find out where the differences between groups exactly occurred.

A rANOVA revealed a significant main effect of set size ($F_{3,195} = 44.205$, $p = .000$), performance group ($F_{2,69} = 21.538$, $p = .000$) and a performance group x set size interaction ($F_{9,208} = 2.798$, $p = .013$). Comparative analyses of the group data were performed using a univariate ANOVA, that was carried out to find out at which set sizes the differences between groups exactly occurred, showed a significant difference between young low and high performer for all set sizes (all p-values $< .05$, Tab. A.7). Similar to young participants the group of elder participants with a high VWM capacity performed significantly better than the group with a low VWM capacity, but only for the set sizes of three to five (all p-values $< .05$). No significant differences between elder high performer and young participants with a poor performance were found in any of the presented set sizes (all p-values $> .05$, Tab. A.7).

4.2.2 *Behavioral data:* Effects of working memory capacity on performance in combined task

To investigate in what sense performance in the memory and filtering task was dependent on the individual WMC, direct and indirect measures of filtering and storage performance (correct rejections, filtering and memory deficit, NFHM hit rate) were correlated with individual WMC that was measured in the pretest. By means of partial correlation the data were controlled for the time of measurement, by including the session (first/second) as a control variable.

Young participants

A significant positive correlation was found between VWM capacity and hit rate in the high memory condition (r = .421, p = .008, Fig. 4.16). The higher the individual

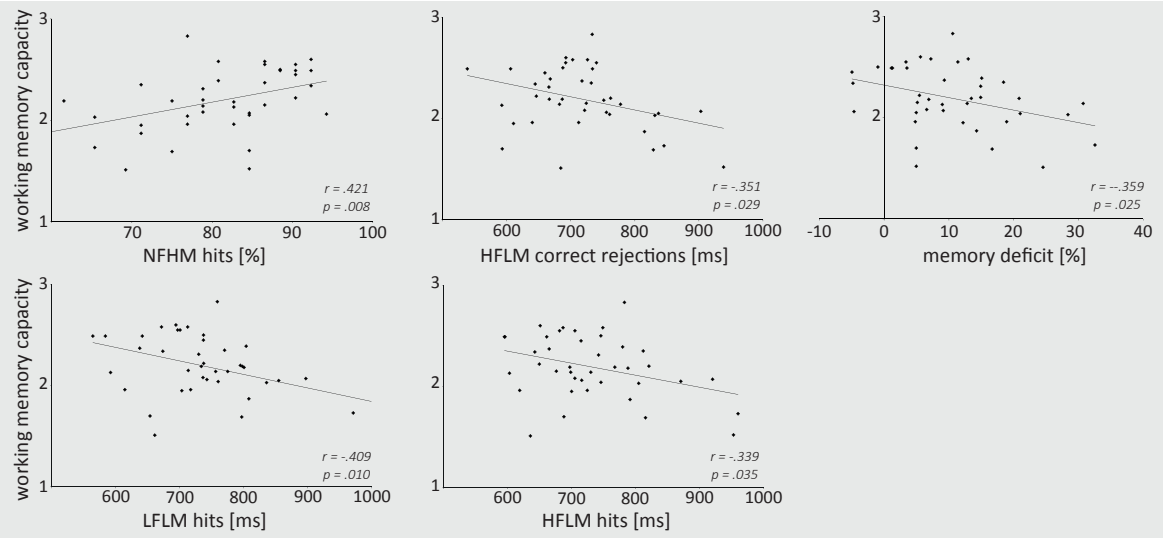

Figure 4.16: Correlation of individual VWM capacity of young with: *Left upper column:* hits (%) in NFHM; *Middle upper column:* response times (ms) of correct rejections in HFLM; *Right upper column:* memory deficit (Δ%); *Left lower column:* response times of hits (ms) in LFLM; *Middle lower column:* response times of hits (ms) in HFLM

VWM capacity was, the better targets were memorized when four rectangles were presented. Furthermore, a higher VWM capacity was associated with faster responses in hits of both filter conditions (LFLM: r = -.409, p = .010; HFLM: r = -.339, p = .035). In addition, increased VWM capacity was correlated with a decreased memory deficit (r = -.359, p = .025). VWM capacity had no significant influence on the amount of correct responses after the distractor was probed but correlated significant negative with response times after probing the strong distractor (r = -.351, p = .029). The p- and r-values can be depicted from Tab. A.8.

Elderly participants

Similar to young participants VWM capacity of elderly was associated with responses in hits of all conditions but this association was positive in contrast to the negative correlation in the younger cohort (NFHM: r = .479, p = .004; LFLM: r = .387, p = .024;

HFLM: r = .434, p = .010, Fig. 4.17). All correlation coefficients and p-values can be depicted from Tab. A.8.

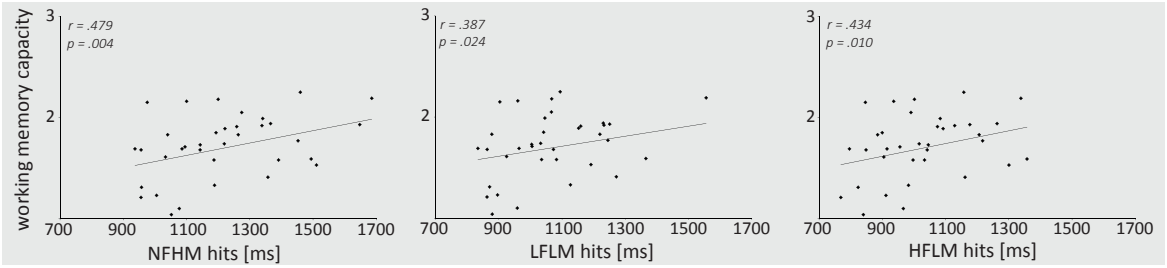

Figure 4.17: Correlation of individual VWM capacity of elderly with: *Left column:* response times of hits (ms) in NFHM; *Middle column:*response times of hits (ms) in LFLM ; *Right column:* response times of hits (ms) in HFLM

Comparison between young and elderly participants

Whereas a high VWM capacity was associated with a better performance in the high memory (no filtering) condition and faster responses in both filter conditions in young this effect was reversed in elderly. In the elderly cohort a higher VWM capacity was reflected in slower responses in all conditions. In addition, in those trials the distractor was probed young participants benefited from a high VWM capacity resulting in a faster rejection. Furthermore, a higher VWM capacity was associated with a lower memory deficit in young only.

4.2.3 *Functional MRI-data:* Effects of working memory capacity on neural correlates of memory and attention

Young participants

Increased filter activity in the left basal ganglia (pallidum) was associated with higher VWM capacity (r = .333, p = .036, Fig. 4.18). No further significant correlations between individual VWM capacity and activation in prior defined memory or filtering related regions could be found (p > .05). All correlation coefficients and p-values can be depicted from Tab. A.9.

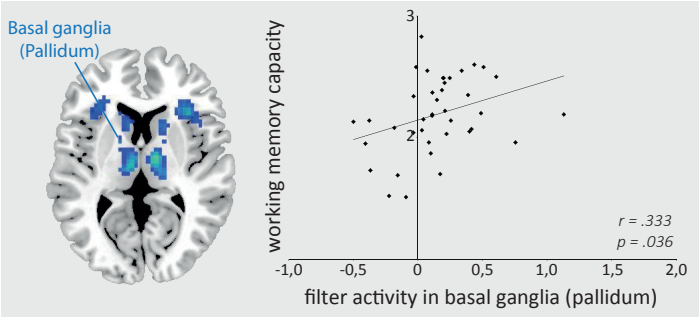

Figure 4.18: Correlation of individual VWM capacity of young with filter activity in left basal ganglia (pallidum)

Elderly participants

A significanct correlation between VWM capacity and effective storage activity was found in the left STC (r = .329, p = .047, Fig. 4.19). VWM capacity was significantly associated with filter activity in the left thalamus (r = .354, p = .032) and right cuneus (r = .376, p = .022). All correlation coefficients and p-values can be depicted from Tab. A.10.

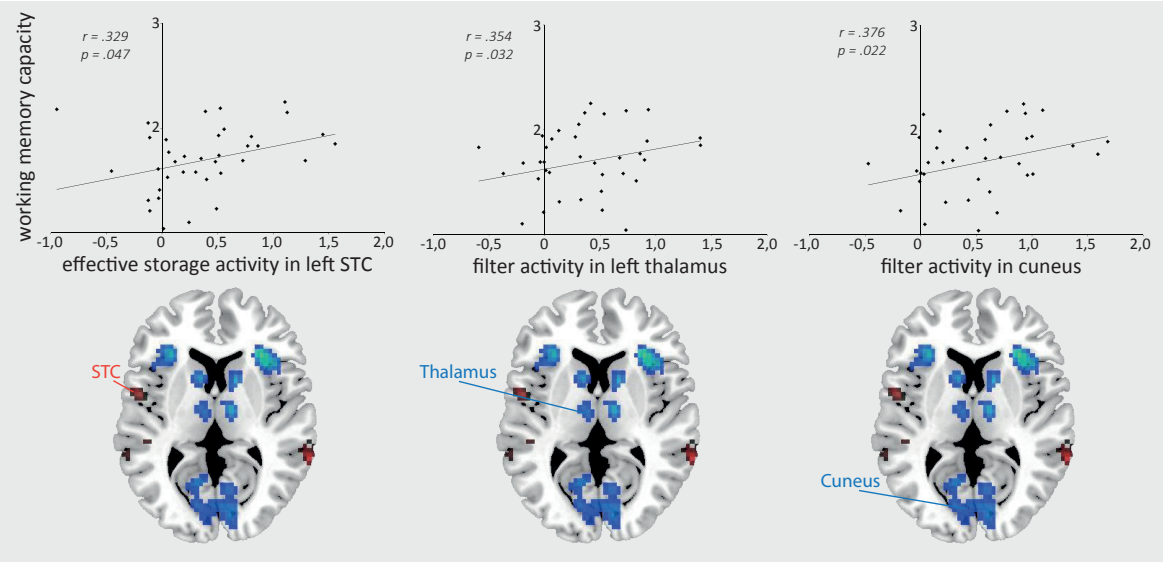

Figure 4.19: Correlation of individual VWM capacity of elderly with: *Left column:* effective storage activity in left STC; *Middle column:* filter activity in left thalamus; *Right column:* filter activity in cuneus

Comparison between young and elderly participants

Individual VWM capacity was associated with filtering related activation in left basal ganglia (pallidum) in the young cohort and with left thalamus and right cuneus in the elderly cohort. Moreover, associations between effective storage activity and VWM capacity were found in left STC in the elderly, but not in young participants.

4.2.4 *Structural MRI-data:* Effects of structural integrity on working memory capacity

Because of significant differences between placebo groups in BF_{vol} of the young participants and SN_{vol} of the elderly participants "placebo group" was included as covariate in all analyses.

Young participants: Effects of SN_{MT} and SN_{vol}

No significant correlations were found between WMC and SN_{MT} (r = .150, p = .363) or SN_{vol} (r = .125, p = .447) of substantia nigra.

Young participants: Effects of BF_{vol}

No significant correlations were found between WMC and BF_{vol} (r = -.031, p = .853).

Elderly participants: Effects of SN_{MT} and SN_{vol}

No significant correlations were found between WMC and SN_{MT} (r = .174, p = .333) or SN_{vol} (r = -.078, p = .665).

Elderly participants: Effects of BF_{vol}

No significant correlations were found between WMC and BF_{vol} (r = -.117, p = .502).

Comparison between young and elderly participants: SN_{MT}, SN_{vol} and BF_{vol}

Associations between WMC and structural measures of the substantia nigra and the basal forebrain were not found in any of the age cohorts.

4.3 Influence of drug administration on memory and filter correlates

4.3.1 *Behavioral data:* Effects of drug administration on performance in combined task

Young participants: Effects of Levodopa administration

Administration of levodopa had neither a significant impact on accuracy of correct rejections nor filter and memory deficit or hit rates of high memory condition in the combined task (all p-values $> .05$, Tab. A.11). Means and standard errors are graphed in Fig. 4.20.

Young participants: Effects of Galantamine administration

Similar to the prior reported results a rANOVA revealed no significant drug effects in the accuracy of correct rejections, filter and memory deficit or hit rates (all p-values $> .05$, Tab. A.12).

Elderly participants: Effects of Levodopa administration

No significant effects of levodopa on performance in the combined task were found in the elderly cohort. See Tab. A.11 for means, F- and p-values and Fig. 4.20 for means and standard errors.

Elderly participants: Effects of Galantamine administration

Administration of galantamine had no significant impact on the hit rate, correct rejections or filter and memory deficit (all p-values $> .05$, Tab. A.12).

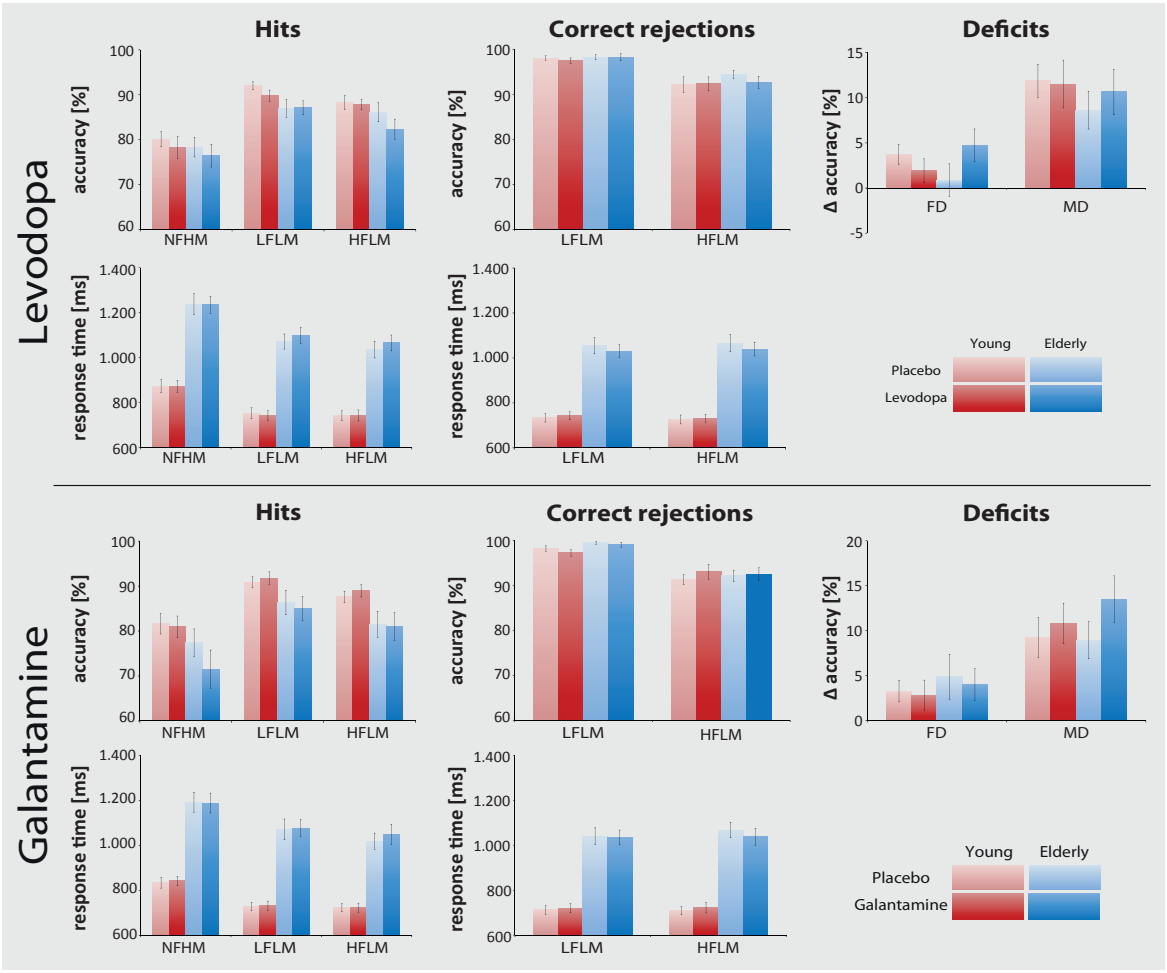

Figure 4.20: Means and standard errors of means for the performance of each age and each drug group (red = young, blue = elderly, bright colors = placebo administration): *Left column:* Group-averaged hits (%) of all conditions and corresponding response times (ms); *Middle column:* Group-averaged correct rejections (%) of LFLM and HFLM condition referring to lure trials and corresponding response times (ms); *Right column:* Group-averaged filter and memory deficit (Δ%)

Comparison between young and elderly participants: Effects of Levodopa administration

RANOVAs with the within factors task (response types) and drug (drug/placebo), the between subject factors age (young/elderly) and time of drug administration (first/second session) revealed no significant levodopa x age interactions (all p-values $> .05$, Tab. 4.6).

Comparison between young and elderly participants: Effects of Galantamine administration

No significant galantamine x age interaction was found in the hit rate, correct rejections or filter and memory deficit (all p-values $> .05$, Tab. 4.6).

Table 4.6: Effects of age and drug administration (galantamine/levodopa) on performance in the combined task indicated by F- and p-values

Response Type		Condition	IE Levodopa x Age F-Value (1,36)	IE Levodopa x Age p-Value	IE Galantamine x Age F-Value (1,34)	IE Galantamine x Age p-Value
Hits	%	NFHM LFLM HFLM	.010	.922	2.016	.165
	ms	NFHM LFLM HFLM	1.941	.172	.504	.483
Correct rejection	%	LFLM HFLM	.227	.637	.173	.680
	ms	LFLM HFLM	1.606	.213	1.135	.295
Filter deficit	Δ%		3.440	.072	.013	.908
Memory deficit	Δ%		.346	.560	.811	.374

IE = Interaction effect

4.3.2 *Behavioral data:* Effects of working memory capacity on drug effects in combined task

To test whether drug effects were dependent on VWM capacity participants were divided into groups of participants with a low and high VWM capacity by median split for each drug group. The medians of each group can be depicted from Tab. 4.7.

Table 4.7: VWM capacity median of each drug group in the cohorts of young and elderly

	Levodopa/Placebo	Galantamine/Placebo
Young	2.15	2.25
Elderly	1.74	1.69

Young participants: Effects of Levodopa administration

A rANOVA with the within factor drug (dopamine/placebo), the between factors performance group (high/low VWM capacity) and drug session (first/second session) revealed no significant dopamine x performance group interaction in any of the tested response types (all p-values $>$ .05). See Tab. A.13 for F- and p-values of statistical analysis.

Young participants: Effects of Galantamine administration

No significant galantamine x performance group interaction was found in any of the tested response types (all p-values $>$ .05). See Tab. A.13 for F- and p-values of statistical analysis.

Elderly participants: Effects of Levodopa administration

A rANOVA revealed no significant dopamine x performance group interaction in any of the tested response types (all p-values $>$ .05). See Tab. A.13 for F- and p-values of statistical analysis.

Elderly participants:Effects of Galantamine administration

A rANOVA revealed no significant galantamine x performance group interaction in any of the tested response types (all p-values $>$ .05). See Tab. A.13 for F- and p-values of statistical analysis.

Comparison between young and elderly participants: Effects of Levodopa administration

A rANOVA with the additional between factor age revealed no significant dopamine x age x performance group interaction (all p-values $>$ .05, Tab. 4.8).

Comparison between young and elderly participants: Effects of Galantamine

A rANOVA with the additional between factor age revealed no significant galantamine x age x performance group interaction (all p-values $> .05$, Tab. 4.8).

Table 4.8: Effects of drug administration (galantamine/levodopa) on performance in the combined task in dependency on VWM capacity performance group (VWMC PG) indicated by F- and p-values

Response Type		Condition	IE Levodopa x VWMC PG x Age F-Value (1,31)	IE Levodopa x VWMC PG x Age p-Value	IE Galantamine x VWMC PG x Age F-Value (1,29)	IE Galantamine x VWMC PG x Age p-Value
Hits	%	NFHM LFLM HFLM	.876	.357	.230	.636
	ms	NFHM LFLM HFLM	1.234	.275	.009	.927
Correct rejection	%	LFLM HFLM	.299	.589	.000	.995
	ms	LFLM HFLM	.080	.779	.390	.538
Filter deficit	Δ%		.145	.706	.513	.480
Memory deficit	Δ%		.000	.996	.056	.815

IE = Interaction effect

4.3.3 *Functional MRI-data:* Effects of drug administration on neural correlates of memory and attention

Young participants: Effects of Levodopa administration

The rANOVA of ROIs from the memory contrast revealed neither a significant main effect of region ($F_{2,36} = 2.178$ $p = .128$) nor drug ($F_{1,18} = 1.382$, $p = .255$) nor a drug x region interaction ($F_{2,36} = .574$, $p = .568$) thus further rANOVAs on data of each region separately were not carried out.

The rANOVA of ROIs from the filter contrast revealed a significant main effect of region ($F_{6,104} = 3.527$, $p = .004$) but no significant main effect of drug ($F_{1,18} = 1.666$, $p = .213$). Because a significant drug x region interaction ($F_{6,109} = 2.222$, $p = .045$) was found further rANOVAs were carried out on data of each region separately. A significant effect of drug was found in the right SPC ($F_{1,18} = 10.008$ $p = .005$) as well as in the right ($F_{1,18} = 5.688$ $p = .028$) and left cerebellum ($F_{1,18} = 5.387$ $p = .032$).

Filter activity in the right SPC and the cerebellum was significantly reduced after administration of levodopa (Fig. 4.21).

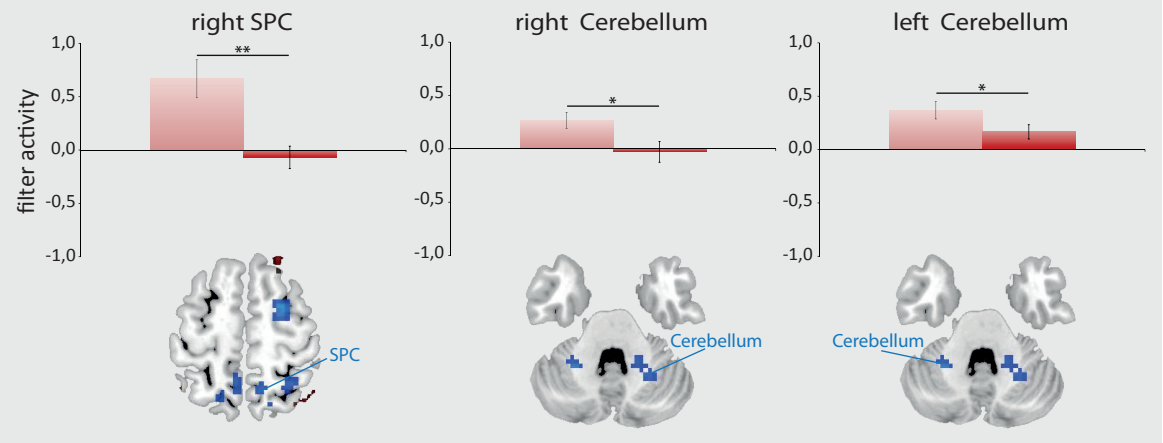

Figure 4.21: Effects of levodopa on filter activity in: *Left column:* right SPC; *Middle and right column:* bilateral Cerebellum in young

Young participants: Effects of Galantamine administration

The rANOVA of ROIs from the memory contrast revealed neither a significant main effect of region ($F_{2,40} = 1.719$, $p = .190$) or drug ($F_{1,18} = 2.762$, $p = .114$) nor a drug x region interaction ($F_{2,41} = .988$, $p = .389$) thus further rANOVAs on data of each region separately were not carried out.

The rANOVA of ROIs from the filter contrast revealed a significant main effect of region ($F_{8,136} = 5.254$, $p = .000$). Whereas a main effect of drug did not reach significance ($F_{1,18} = .258$, $p = .617$) drug and region were significantly interacted ($F_{7,118} = 2.654$, $p = .016$) thus further rANOVAs on data of each region separately were carried out. The same region in the right SPC that was effected by levodopa showed reduced filter activity as well after galantamine administration ($F_{1,18} = 8.575$, $p = .009$, Fig. 4.22). Similarly filter activity was significantly reduced in the left STC ($F_{1,18} = 11.673$, $p = .003$) and increased in the left fusiform gyrus after galantamine administration ($F_{1,18} = 4.681$, $p = .044$).

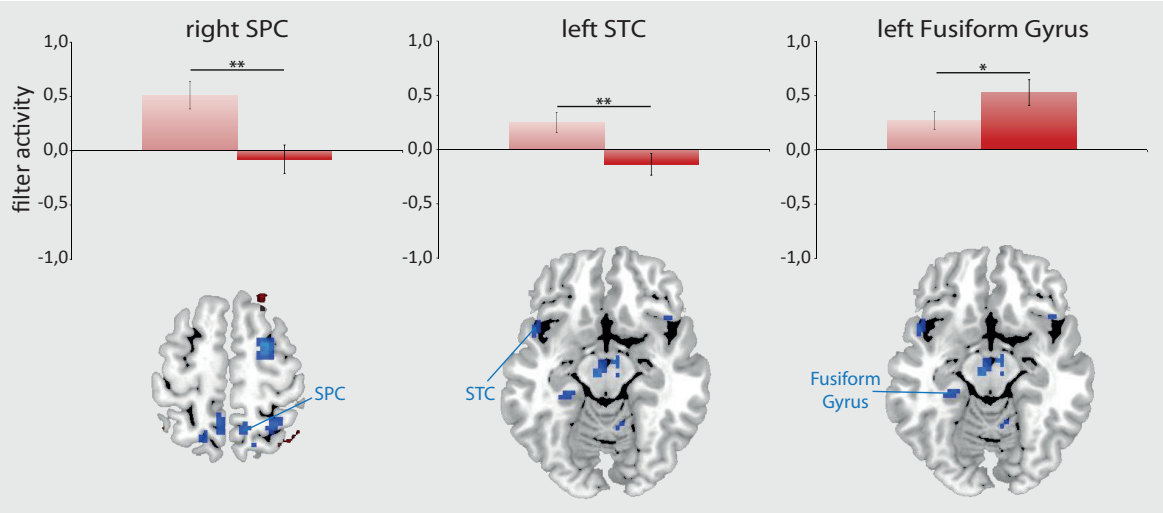

Figure 4.22: Effects of galantamine on filter activity in: *Left column:* right SPC; *Middle column:* left STC; *Right column:* left fusiform gyrus in young

Elderly participants: Effects of Levodopa administration

The rANOVA of ROIs from the memory contrast revealed neither a significant main effect of region ($F_{4,68} = 1.606$, $p = .186$) or drug ($F_{1,18} = 3.236$, $p = .089$) nor a drug x region interaction ($F_{3,57} = 2.205$, $p = .094$) thus further rANOVAs on data of each region separately were not carried out.

The rANOVA of ROIs from the filter contrast revealed a significant main effect of region ($F_{26,468} = 2.090$, $p = .001$) but neither a significant main effect of drug ($F_{1,18} = 1.079$, $p = .313$) nor a drug x region interaction ($F_{26,468} = 1.207$, $p = .223$) thus further rANOVAs on data of each region separately were not carried out.

Elderly participants: Effects of Galantamine administration

The rANOVA of ROIs from the memory contrast revealed neither a significant main effect of region ($F_{3,50} = 1.464$, $p = .234$) or drug ($F_{1,16} = .403$, $p = .535$) nor a drug x region interaction ($F_{3,50} = .996$, $p = .405$) thus further rANOVAs on data of each region separately were not carried out.

The rANOVA of ROIs from the filter contrast revealed a significant main effect of region ($F_{26,416} = 2.717$, $p = .000$) but neither a significant main effect of drug

($F_{1,16} = 1.570$, p = .228) nor a drug x region interaction ($F_{26,416} = 1.163$, p = .267) thus further rANOVAs on data of each region separately were not carried out.

Comparison between young and elderly participants: Effects of Levodopa administration

Statistical analysis revealed no significant effect of levodopa on ß-values on effective storage activity in young and elderly participants (all p-values > .05). A significant effect of levodopa administration on filter activity was found in right SPC and bilateral cerebellum in young participants.

Comparison between young and elderly participants: Effects of Galantamine administration

Galantamine administration had no effect on effective storage activity in any of the age cohorts, (all p-values > .05) but had an impact on filter activity in right SPC, left STC and left fusiform gyrus in young.

4.3.4 *Structural MRI data:* Effects of structural integrity of substantia nigra and basal forebrain on drug effects in the combined task

Young participants: Effects of Levodopa administration in relation to SN_{MT}, SN_{vol} and BF_{vol}

A rANOVA with the within factor drug (levodopa/placebo), the between factor drug session (first/second) and the covariates SN_{MT}, SN_{vol} and BF_{vol} revealed no significant interaction between levodopa and structural measures (all p-values > .05, Tab. A.14).

Young participants: Effects of Galantamine administration in relation to SN_{MT}, SN_{vol} and BF_{vol}

No significant interaction between galantamine and structural measures of substantia nigra and basal forebrain were found (all p-values > .05, Tab. A.15) except an galantamine x SN_{vol} interaction in response times of correct rejections ($F_{1,17}$ = 6.447, p = .021). This effect was found in the low filtering condition ($F_{1,17}$ = 5.599, p = .030) as well as in the high filtering condition ($F_{1,17}$ = 4.523, p = .048). Participants with a higher SN_{vol} responded slower during lure trials after galantamine administration whereas this effect was reversed in participants with a lower SN_{vol} (Fig. 4.23).

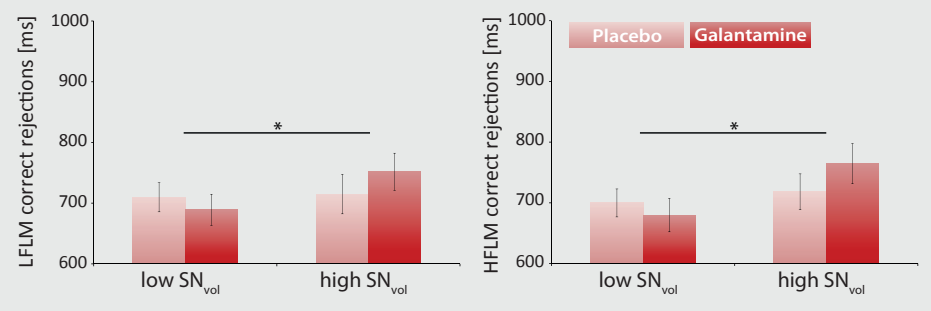

Figure 4.23: Interaction between SN_{vol} and galantamine effects in young on response times (ms) of correct rejections in: *Left column:* LFLM; *Right column:* HFLM; note that groups were separated by median split based on SN_{vol} for visualization

Elderly participants: Effects of Levodopa administration in relation to SN_{MT}, SN_{vol} and BF_{vol}

No significant interactions between levodopa and structural measures of substantia nigra and basal forebrain were found (all p-values > .05, Tab. A.14).

Elderly participants: Effects of Galantamine administration in relation to SN_{MT}, SN_{vol} and BF_{vol}

A rANOVA revealed a significant galantamine x SN_{MT} interaction in hit rates ($F_{1,14}$ = 7.034, p = .021) and in the correct rejections ($F_{1,14}$ = 13.093, p = .004, Fig. 4.24). The latter effect was not significant in correct rejections of any condition after post hoc analysis (LFLM: $F_{1,14}$ = 2.943, p = .112, HFLM: $F_{1,14}$ = 1.891, p = .194). Post hoc

analysis of hit rates revealed a significant galantamine x SN_{MT} interaction in NFHM ($F_{1,14}$ = 5.778, p = .033) and LFLM ($F_{1,14}$ = 5.876, p = .032) but not in HFLM ($F_{1,14}$ = 1.779, p = .207) condition. In addition to the reported effects, galantamine showed an influence on filter deficit in dependency to BF_{vol} ($F_{1,15}$ = 6.063, p = .029).

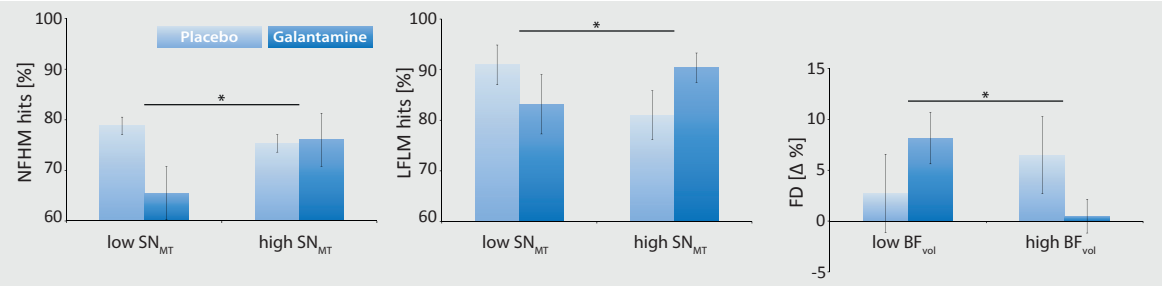

Figure 4.24: Interaction between SN_{MT} and galantamine effects in elderly on hits (%) in: *Left column:* NFHM; *Middle column:* LFLM; *Right Column:* Interaction between BF_{vol} and galantamine effects on filter deficit (Δ%) in elderly; note that groups were separated by median split based on SN_{MT} and BF_{vol} for visualization

Comparison between young and elderly participants: Effects of Levodopa/Galantamine administration in relation to SN_{MT}, SN_{vol} and BF_{vol}

Effects of levodopa on behavioral performance in the combined task was not associated with SN_{MT}/SN_{vol} or BF_{vol} in any of the tested age cohorts. In contrast, different galantamine effects on response times in correct rejections were found with regard to SN_{vol} in young. Elderly participants with a high SN_{MT} responded more accurate in hits of NFHM and LFLM condition after galantamine administration whereas this effect was reversed in elderly participants with a low SN_{MT}. Moreover, galantamine effects on filter deficits were associated with BF_{vol} in elderly.

4.4 Influence of genetic diversity on memory and filter correlates

The allele and genotype frequencies from all polymorphisms for each age cohort are listed in Tab. 4.9. All genotype frequencies were in the Hardy-Weinberg equilibrium.

Table 4.9: Genotype (GF) and allele frequencies (AF) in the group of young and elderly participants for DBH, COMT and CHRNA4 polymorphisms

Young								
	COMT			**DBH**			**CHRNA4**	
Alleles	**GF**	**AF**	**Alleles**	**GF**	**AF**	**Alleles**	**GF**	**AF**
mm	.30	.56	**GG**	.18	.44	**CC**	.23	.51
mv	.53	-	**AG**	.51	-	**CT**	.56	-
vv	.18	.44	**AA**	.31	.56	**TT**	.21	.49
Elderly								
	COMT			**DBH**			**CHRNA4**	
Alleles	**GF**	**AF**	**Alleles**	**GF**	**AF**	**Alleles**	**GF**	**AF**
mm	.19	.44	**GG**	.28	.56	**CC**	.17	.49
mv	.50	-	**AG**	.56	-	**CT**	.63	-
vv	.31	.56	**AA**	.17	.44	**TT**	.20	.51

4.4.1 *Behavioral data:* Effects of genetic diversity on performance on combined task

Young participants: Effects of DBH, COMT and CHRNA4 polymorphisms

RANOVAS on response types and univariate ANOVAs on filter and memory deficit revealed neither a significant main effect of DBH, COMT nor CHRNA4 for the different response types (all p-values $>$ .05, Tab. A.16, A.17 and A.18).

Elderly participants: Effects of DBH, COMT and CHRNA4 polymorphisms

Similar to results in the young cohort no sognificant differences between polymoprphims groups with regard to performance in the combined task were found in elderly (all p-values $>$ .05, Tab. A.16, A.17 and A.18).

Comparison between young and elderly participants: Effects of DBH, COMT and CHRNA4 polymorphisms

No significant differences between age cohorts were found in performance in the combined task with regard to DBH, COMT or CHRNA4 polymorphisms (all p-values $> .05$, Tab. A.19).

4.4.2 *Behavioral data:* Effects of genetic diversity on working memory capacity

Young participants: Effects of DBH, COMT and CHRNA4 polymorphisms

A univariate ANOVA revealed no significant difference in VWM capacity between the DBH ($F_{2,36}$ =.916, p = .409), COMT ($F_{2,37}$ =.224, p = .800) or CHRNA4 polymorphisms groups ($F_{2,37}$ =.762, p = .474).

Elderly participants: Effects of DBH, COMT and CHRNA4 polymorphisms

No significant difference in VWM capacity was found between DBH ($F_{2,30}$ =.239, p = .789), COMT ($F_{2,30}$ =1.061, p = .359) or CHRNA4 polymorphism groups ($F_{2,29}$ = 2.065, p = .145).

Comparison between young and elderly participants: Effects of DBH, COMT and CHRNA4 polymorphisms

A univariate ANOVA with the additional factor age revealed no significant interactions between age and DBH ($F_{2,63}$ =.745, p = .479), COMT ($F_{2,64}$ = .541, p = .585) or CHRNA4 ($F_{2,62}$ =1.307, p = .278) in VWM capacity.

4.4.3 *Functional MRI-data:* Effects of genetic diversity on neural correlates of memory and attention

Young participants: Effects of DBH polymorphism

A rANOVA of ß-values from the memory contrast revealed a significant main effect of region ($F_{2,72}$ = 3.430, p = .038) but no significant effect of DBH ($F_{2,36}$ = 1.559, p = .224) or a significant region x DBH interaction ($F_{4,72}$ = 1.292, p = .281).
A rANOVA of filter activity with the within factor region and the between factor DBH revealed a significant effect of region ($F_{7,253}$ = 3.866, p = .00) but neither a significant main effect of DBH ($F_{2,36}$ = 1.534, p = .229) nor a DBH x region interaction ($F_{14,153}$ = .906, p = .554).

Young participants: Effects of COMT polymorphism

A rANOVA on effective storage activity revealed neither a significant effect of region ($F_{2,74}$ = 2.880, p = .062) or COMT ($F_{2,37}$ = .026, p = .974) nor a COMT x region interaction ($F_{4,74}$ = .712, p = .586) thus data were not further analyzed.
A rANOVA on ß-values from the filter contrast revealed a significant effect of region ($F_{7,276}$ = 2.381, p = .000) but neither a significant main effect of COMT ($F_{2,37}$ = 1.697, p = .197) nor a COMT x region interaction ($F_{15,276}$ = .699, p = .785) thus data were not further analyzed.

Young participants: Effects of CHRNA4 polymorphism

A rANOVA revealed a significant effect of region ($F_{2,72}$ = 5.696, p = .005) but neither a significant main effect of CHRNA4 ($F_{2,36}$ = .461, p = .634) nor a CHRNA4 x region interaction ($F_{4,72}$ = 1.543, p = .199) thus data were not further analyzed.
A rANOVA on ß-values from the filter contrast revealed a significant effect of region ($F_{7,252}$ = 3.628, p = .001) but neither a significant main effect of CHRNA4 ($F_{2,36}$ = .539, p = .588) nor a CHRNA4 x region interaction ($F_{14,252}$ = 1.606, p = .078) thus data were not further analyzed.

Elderly participants: Effects of DBH polymorphism

A rANOVA on effective storage activity revealed neither a main effect of region ($F_{4,136} = 2.249$, $p = .063$), DBH ($F_{2,32} = 1.062$, $p = .358$) nor a region x DBH interaction ($F_{9,136} = 1.401$, $p = .197$).
In terms of filter activity a significant effect of region ($F_{9,287} = 2.299$, $p = .018$) but neither a main effect of DBH ($F_{2,33} = 1.837$, $p = .175$) nor an region x DBH ($F_{17,287} = .588$, $p = .903$) interaction was found.

Elderly participants: Effects of COMT polymorphism

A rANOVA on effective storage activity revealed neither a main effect of region ($F_{4,129} = 1.064$, $p = .377$), COMT ($F_{2,32} = .745$, $p = .483$) nor a region x COMT interaction ($F_{8,129} = .574$, $p = .800$).
A significant main effect of region ($F_{9,189} = 2.362$, $p = .015$) but neither a main effect of COMT ($F_{2,33} = 1.162$, $p = .325$) nor a region x COMT interaction ($F_{18,289} = .853$, $p = .634$) was found in filter activity.

Elderly participants: Effects of CHRNA4 polymorphism

A rANOVA on effective storage activity revealed neither a main effect of region ($F_{4,128} = 1.840$, $p = .123$) nor of CHRNA4 ($F_{2,31} = .940$, $p = .402$) but a region x CHRNA4 interaction ($F_{8,128} = 2.177$, $p = .032$). A subsequent ANOVA that was carried out for each region separately showed that this effect was due to a significant difference between CHRNA4 polymorphism carriers in the anterior part of the left aIPC ($F_{2,31} = 4.994$, $p = .013$, Fig. 4.25). CC carriers showed significantly higher effective storage activity in left aIPC than CT ($p = .019$) and TT carriers ($p = .026$).
A significant effect of region ($F_{9,282} = 2.256$, $p = .020$) but no main effect of CHRNA4 ($F_{2,32} = .964$, $p = .392$) was found with regard to filter activity. In addition, no region x CHRNA4 interaction was found ($F_{18,282} = 1.282$, $p = .200$).

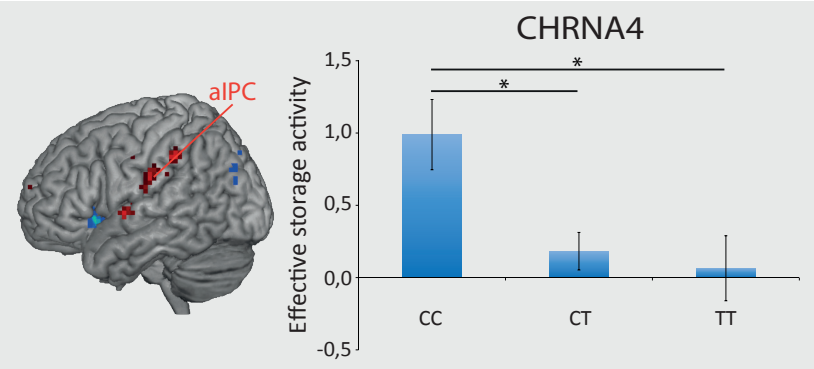

Figure 4.25: Differences in effective storage activity of left aIPC between CHRNA4 polymorphism carrier in elderly

Comparison between young and elderly participants: DBH, COMT and CHRNA4

No significant differences in effective storage activity or filter activity between DBH, COMT or CHRNA4 allele carriers were found in any of the age groups.

4.4.4 *Structural MRI data:* Effects of genetic diversity on structural integrity

Because of significant differences between placebo groups in BF_{vol} of the young participants and SN_{vol} of the elderly participants "placebo group" was included as covariate in all analyses.

Young participants: Effects of DBH polymorphism in relation to SN_{MT}, SN_{vol} and BF_{vol}

The different DBH polymorphism carriers did neither differ in SN_{vol} ($F_{2,33} = .859$, $p = .433$), SN_{MT} ($F_{2,33} = .881$, $p = .424$) or BF_{vol} ($F_{2,33} = 1.165$, $p = .325$). A significant DBH x placebo group interaction was neither found in SN_{vol} ($F_{2,33} = .309$, $p = .736$), SN_{MT} ($F_{2,33} = .171$, $p = .844$) or BF_{vol} ($F_{2,33} = .007$, $p = .993$).

Young participants: Effects of COMT polymorphism in relation to SN_{MT}, SN_{vol} and BF_{vol}

COMT allele carriers showed neither significant differences in SN_{vol} ($F_{2,34} = 2.628$, $p = .087$) nor in SN_{MT} ($F_{2,34} = .849$, $p = .437$) or BF_{vol} ($F_{2,34} = 1.715$, $p = .195$). A significant COMT x placebo group interaction was neither found in SN_{vol} ($F_{2,34} = 1.402$, $p = .260$) nor in SN_{MT} ($F_{2,34} = 1.126$, $p = .336$) or in BF_{vol} ($F_{2,34} = 1.069$, $p = .354$).

Young participants: Effects of CHRNA4 polymorphism in relation to SN_{MT}, SN_{vol} and BF_{vol}

The different CHRNA4 polymorphism carriers did not differ in SN_{vol} ($F_{2,33} = .485$, $p = .620$) nor in SN_{MT} ($F_{2,33} = 2.992$, $p = .064$) but in BF_{vol} ($F_{2,33} = 7.432$, $p = .002$). Homozygote CC allele carriers had a significantly lower BF_{vol} ($.28 \pm .02$ SEM) than heterozygote CT allele carriers ($.36 \pm .01$ SEM, $p = .002$) and a trend towards a lower BF_{vol} than TT allele carriers have ($.337 \pm .02$ SEM, $p = .064$, Fig. 4.26).

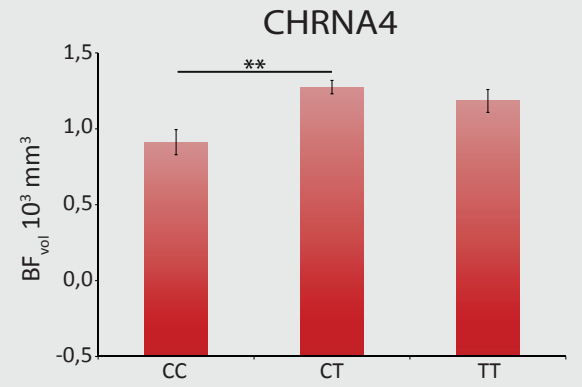

Figure 4.26: Differences in BF_{vol} between CHRNA4 polymorphism carrier in young

A significant CHRNA4 x placebo group interaction was neither found in SN_{vol} ($F_{2,33} = .005$, $p = .995$) nor in SN_{MT} ($F_{2,33} = 1.141$, $p = .332$) or in BF_{vol} ($F_{2,33} = .100$, $p = .905$).

Elderly participants: Effects of DBH polymorphism in relation to SN_{MT}, SN_{vol} and BF_{vol}

The different DBH polymorphism carriers did neither differ in SN_{vol} ($F_{2,28}$ = .294, p = .748), SN_{MT} ($F_{2,28}$ = .843, p = .441) nor BF_{vol} ($F_{2,30}$ = 1.333, p = .279). A significant DBH x placebo group interaction was neither found in SN_{vol} ($F_{2,28}$ = 1.335, p = .279) nor in SN_{MT} ($F_{2,28}$ = 1.736, p = .195) or in BF_{vol} ($F_{2,30}$ = .747, p = .482).

Elderly participants: Effects of COMT polymorphism in relation to SN_{MT}, SN_{vol} and BF_{vol}

COMT allele carriers showed no significant differences in SN_{vol} ($F_{2,28}$ = .249, p = .781), SN_{MT} ($F_{2,28}$ = .479, p = .624) or BF_{vol} ($F_{2,30}$ = 1.263, p = .297). A significant COMT x placebo group interaction was neither found in SN_{vol} ($F_{2,28}$ = .733, p = .489) nor in SN_{MT} ($F_{2,28}$ = .670, p = .520) or in BF_{vol} ($F_{2,30}$ = .749 p = .481).

Elderly participants: Effects of CHRNA4 polymorphism in relation to SN_{MT}, SN_{vol} and BF_{vol}

The different CHRNA4 polymorphism carriers did not differ in SN_{vol} ($F_{2,27}$ = 2.091, p = .143), SN_{MT}($F_{2,27}$ = .315, p = .733) or BF_{vol} ($F_{2,29}$ = .706, p = .502). A significant CHRNA4 x placebo group interaction was neither found in SN_{vol} ($F_{2,27}$ = 2.302, p = .119) nor in SN_{MT} ($F_{2,27}$ = .419, p = .662) or in BF_{vol} ($F_{2,29}$ = 1.833 p = .178).

Comparison between young and elderly participants: Effects of DBH, COMT and CHRNA4 polymorohisms in relation to SN_{MT}, SN_{vol} and BF_{vol}

No significant differences in SN_{vol} and BF_{vol} or SN_{MT} were found between polymorphism groups of DBH, COMT and CHRNA4 in the young and elderly participants except a significant difference between CHRNA4 allele groups in BF_{vol} in the young cohort. These difference was reflected in a lower BF_{vol} in CC carriers than in CT carriers.

5 Discussion

The present thesis aimed at investigating the behavioral and neural basis of selective attention and information storage within VWM in young and elderly humans. A special focus was placed on the role of the neurotransmitters dopamine and acetylcholine in these processes. For that purpose, neurotransmitter levels were modulated by means of drug administration. In addition, information about gene variations pointing to individual differences in neurotransmitter levels in the brain was gathered. Alongside the determination of gene variations, individual integrity of brain structures that constitute main nodes for the synthesis of dopamine and acetylcholine were analyzed.
In the first part of the discussion, behavioral and neural correlates of VWM and selective attention that were defined in this thesis will be discussed as well as structural measures (5.1). In the second part, the influence of the individual VWM capacity on the described correlates will be discussed (5.2). The influence of neurotransmitter modulating drugs on the defined correlates will be subsequently discussed (5.3), followed by the discussion of the effects in relation to the genetic background of the participants (5.4).

5.1 Definition of memory and filter correlates

For the purpose of analyzing behavioral and neural processes underlying working memory and selective filtering of information, a delayed matching-to-sample paradigm was developed which comprised a modulation of memory and filtering demands whilst the perceptual input was kept constant. A higher memory load was leading to the worst

performance in both age groups in comparison to the low memory conditions (Fig. 4.1, p. 66 and Fig. 4.2, p. 69). In terms of filter modulation, performance in the low filtering condition was better than in the high filtering condition, which was not only reflected in hit rates but also in an interference effect in correct rejections: When the probe was on a position formerly occupied by a distractor, accuracy was higher in LFLM condition in comparison to the HFLM condition across both age cohorts. In the cohort of elderly participants the effect of filter modulation was observed in correct rejections only. In terms of response times the filter modulation did not evoke any differences in young participants but in elderly participants in hit rates. The latter showed the fastest responses in the high filtering condition, pointing to a speed-accuracy trade-off. Compared to the young participants, elderly showed impairments in performance in both filtering conditions reflected in lower hit rates (Fig. 4.3, p. 72). This impairment was neither seen in correct rejections nor in filter deficit scores but in higher response times in elder participants in hit rates and correct rejections across all conditions. The filter impairment in hit rates observed only in elderly could point to an interference effect of distractors when memory load is low but not to a filter deficit per se. This result supports the perceptual load theory of Lavie and colleagues (Lavie & Tsal, 1994; Lavie, 1995; Lavie & De Fockert, 2005) postulating, that a low load of relevant information is leading to a spread of spared resources to irrelevant information whereas a high load of relevant information prevents from distraction. The impairment of elderly seems to reflect a stronger tendency of irrelevant information to utilize left over resources but this cannot be directly proven because a corresponding task with high memory and high filtering demands was not included in this paradigm. The idea that distractors were more often memorized as targets in elderly can be excludedbased on a lack of a significant age effect in correct rejections. This leads to two possibilities: On the one hand, location of distractors might be memorized in addition to location of targets as a strategy by collecting additional information to perform the task which would explain the missing age effects in correct rejections. The memorized distractors might have interfered with the memorized target because the total

memory load was high. On the other hand, distractors might not be memorized at all, neither as distractors nor as targets. But again this can be excluded based on the interference effect of the strong distractor in correct rejections. The exact mechanisms leading to the age effect in hit rates cannot be fully understood but the results clearly show that elderly participants are not impaired in filtering per se. Support for this assumption comes from a study showing that elderly are just delayed in filtering irrelevant information in contrast to young participants (Jost *et al.*, 2011). In this study, age differences were found in the CDA during a delayed matching-to-sample paradigm in the early retention phase. A few milliseconds after stimulus onset the CDA was indistinguishable from the CDA of young participants. The same effect was found in the filter score - a difference in EEG amplitude between a condition in which one item had to be memorized and two had to be ignored and a condition in which three items had to be memorized - pointing to a delayed filtering instead of an impaired filtering mechanism.

To shed more light onto the underlying processes of working memory and attention and get a better understanding of age effects on these processes, a closer look should be taken on fMRI data. The memory contrast was defined as difference in ß-values between the high memory and high filtering condition. This memory contrast was chosen because both conditions had exactly the same visual input and, therefore, the LFLM condition was not included into the contrast analysis. However, conjunction analyses (not presented in this thesis) of both filtering conditions contrasted against the high memory condition (NFHM > (LFLM + HFLM) and vice versa revealed similar brain regions as the pairwise contrasts, supporting the reliability of the present results. In the memory contrast precuneus as well as anterior and posterior parts of right IPC emerged in young participants (Fig. 4.4, p. 73). In elderly participants the right pTC and left STC, left PHC and cingulate gyrus were active in addition to anterior parts of left IPC and a huge cluster in right IPC with a peak in posterior IPC (Fig. 4.7, p. 77).

The involvement of the right IPC during memory processes in both age groups is not surprising and was found by other researchers as well (Todd & Marois, 2004, 2005; Xu & Chun, 2005). Likewise, the precuneus has been reported to be involved in storage of verbal (LaBar *et al.*, 1999) and visuo-spatial information (Raabe *et al.*, 2013). The TC which was found in elderly only in the present study was reported to be involved in memory processes in earlier studies as well. Sustained responses to stimuli even after withdrawal of these, were found besides PFC and PC in TC (Miller & Desimone, 1994). As part of the ventral pathway which is known to be involved in the processing of objects instead of locations, the TC is found to be active during the encoding of objects (Ranganath *et al.*, 2004). The functional role of the cingulate gyrus especially during memory is not well studied. Its posterior part, which was found in this study during memory processes, was previously found to be involved in autobiographical episodic memory (Maddock *et al.*, 2001) and during recognition of words, objects and places (Heun *et al.*, 2005; Sugiura *et al.*, 2005). Furthermore, the size of the posterior cingulate gyrus was correlated with several factors in a memory test including verbal and non-verbal memory capacity and errors in the visual recall of geometric objects (Kozlovskiy *et al.*, 2012). In addition to the cingulate gyrus, the PHC was also found to be involved in memory processing in the elderly only. Despite a subregion (PPA), which is involved in recognition of environments and navigation, the PHC was reported to play a role during the encoding period of working memory tasks (Schon *et al.*, 2004; Olsen *et al.*, 2009).

At first sight the brain regions found in young and elderly participants during memory are more or less in line with the results of several earlier studies, but correlation analyses with behavioral data sketch a more complex picture. For further analyses of fMRI data the difference between ß-values of the high memory and the high filtering condition was calculated. This activity difference was referred to as “effective storage activity” based on the assumption that a brain region involved in the storage of information should show a stronger hemodynamic response when the memory demands are high. Hemodynamic responses in the high filtering (low memory) condition should

therefore be similar to responses in the high memory condition in case distractors were memorized, resulting in a low ß-value difference or effective storage activity between conditions. When distractors are successfully ignored, memory load should be low and accordingly hemodynamic responses should reveal to a high effective storage activity. Whereas an increase in activity difference in precuneus was attending a higher memory deficit in younger participants, an increase in the posterior part of right IPC was associated with a lower hit rate in the LFLM condition only (Fig. 4.11, p. 82). The finding of an increased activity difference in precuneus, which was associated with an increased memory deficit in younger participants, was unexpected and does not fit into the proposed storage model. It is likely that the correlation in precuneus was mainly driven by increased activity during the high memory condition rather than during the filtering condition and thus reflects a brain region involved in memory only. Similarly, an increased activity difference in the posterior part of IPC, which was associated with a poor accuracy in hit rate in the LFLM condition, can hardly be explained with the proposed filter model. In addition to the reported findings, activity difference in the anterior part of IPC was neither correlated with direct nor indirect behavioral measures of working memory performance in any of the age groups. Instead load dependent activity in aIPC was related to successfully avoiding to unnecessarily store distractors in memory, reflected in significant correlations with accuracy and response times in correct rejections of the high filtering condition (Fig. 4.11, p. 82 and Fig. 4.12, p. 83). This association was found in young participants in right aIPC and in elderly in left aIPC. The correlation might be present in right aIPC in elderly as well but the peak of the huge cluster was in posterior regions, so this region was analyzed only. The results found in both age cohorts support the direct interaction between filtering ability and memory storage in IPC which has not been shown before.

Looking at the activity patterns of the anterior and posterior part of right and left IPC in both age groups, the high memory condition evoked the strongest signal increase, whereas the low filtering condition evoked a small signal increase. This pattern is consistent with the IPC's assumed role as storage related brain region. Here, however,

the presence of strong distractors actually led to suppressed activity (negative ß-values) with respect to the other two conditions. This observation can hardly be reconciled with the idea of a pure storage related region. Given that the strong distractors were more likely to be unnecessarily stored (McNab & Klingberg, 2007), a stronger signal in the high filtering than in the low filtering condition would have been expected. The activation patterns in the aIPC region are somewhat more difficult to interpret as only negative values were observed. The deactivation in the presence of strong distractors seems to reflect a suppression of task irrelevant information. This is supported by the correlation of effective storage activity with correct rejections. Participants, who showed more suppression of right or left anterior IPC activity during the presentation of strong distractors, more often correctly rejected lures, i.e. pressed the no button to probes that were presented on former distractor locations. The present findings support the idea of the IPC being more than a mere storage node (Matsuyoshi *et al.*, 2012; Riggall & Postle, 2012). Rather it seems also to be involved in actively filtering out irrelevant information (Vogel *et al.*, 2005). Suppressed activity during focused attention has been well described for visual areas coding irrelevant regions of the visual field (e.g. Serences *et al.*, 2004; Müller & Kleinschmidt, 2004; Gazzaley *et al.*, 2005b; Müller & Ebeling, 2008; Heinemann *et al.*, 2009). The finding of parietal deactivation during the encoding of targets in the presence of strong distractors in the present study might, therefore, also reflect suppression of irrelevant information, possibly modulated by frontal areas (Hopfinger *et al.*, 2000b).

Together these findings suggest, that at least parts of the IPC are not only involved in memory storage but also in the filtering process, whereby the observed deactivation during the presence of strong distractors might reflect a suppression of this irrelevant information. In line with the present findings, in a recent brain lesion study it was found, that posterior parietal lesions entail difficulties in distractor filtering (Friedman-Hill *et al.*, 2003). In addition, several researchers proposed the IPC as the source of attentional control that up and down modulates activity in retinotopic visual cortex (Hopfinger *et al.*, 2000b; Vandenberghe *et al.*, 2001; Müller *et al.*, 2003; Corbetta

et al., 2005). The correlation with performance in lure trials only in the anterior part of IPC in both age cohorts might point to a further functional segregation within the IPC that should be followed in future studies which include retinotopic mapping to delineate subregions of IPC in more detail (e.g. Silver & Kastner, 2009). A functional segregation is also supported by the posterior IPC being associated with performance in the LFLM condition in this thesis. The finding of precuneus during the memory contrast and that activity was predictive of memory deficits in young participants was unexpected and points to a stronger role of this region during memory processes than supposed.

The hemispheric asymmetry found in IPC in young participants during working memory is often reported but explanations for this specialization are vague. Sheremata and colleagues (2010) conducted a classical delayed matching-to-sample task and compared performance to activity in visuotopic IPC regions. Whereas BOLD activity in left IPC was mainly driven by a memory load increase in the right visual field, activity in the right hemisphere was driven by load increases of the whole visual field. The authors proposed a "dual-input" hypothesis in an attempt to explain the hemispheric asymmetry. This hypothesis states that right and left IPC receive visual inputs from the contralateral visual field in a bottom up manner but that right IPS receives mnemonic information from both visual fields in addition. This hypothesis cannot be tested with the paradigm used in this thesis as stimuli were displayed over the whole display, but it constitutes a conceivable explanation for the strong activation in right IPC during memory. The present results are also in line with the hemispatial neglect syndrome. Patients suffering from neglect have impairments in the processing of one visual field because of lesions (e.g. evoked by stroke) in the contralateral hemisphere. The majority of hemineglect patients are suffering from injuries in tempoparietal brain regions restricted to the right hemisphere, leading to neglect in the contralateral field (Vallar, 1998; Pouget & Driver, 2000; Doricchi *et al.*, 2008). With regard the present results, damage in left parietal cortex might be compensated by right parietal cortex, pro-

cessing information from both visual fields. In contrast damage to the right parietal cortex cannot be compensated leading to the hemispatial neglect.

The hemispheric asymmetry can also be explained from an aging perspective. Often observed neural changes during healthy aging are reflected in a decrease in specificity for ventral and dorsal processing pathways (Schiavetto *et al.*, 2002; Cabeza *et al.*, 2004) called "dedifferentiation". This dedifferentiation is not only reflected in an unspecific recruitment of brain regions but also in a “delateralization” of formerly functional lateralized brain regions (Reuter-Lorenz *et al.*, 2000; Nielson *et al.*, 2002; Cabeza *et al.*, 2002; Morcom *et al.*, 2003). For example, Morcom and colleagues (2003) found activity in left PFC during recognition of words in young participants, whereas activity was spread over both hemispheres in elderly. Right lateralized activity in prefrontal and parietal regions in young participants was observed during response inhibition in a different study and was found to be bilateral in elderly (Nielson *et al.*, 2002). Following this studies, dedifferentiation during healthy aging might be the mechanism behind the finding of bilateral IPC during the memory contrast in the elderly and right IPC only in the young participants in the present thesis. Similar results were found during filtering.

By contrasting brain activation that occurred during the high filtering condition with activation during the high memory condition, filter activity could be assessed. Common brain regions that were involved in the filtering process in both age groups were the bilateral insulae, bilateral thalami, bilateral basal ganglia (Striatum/ Caudate Ncl.), right FEF, right OCC (V3) and right SPC (Fig. 4.10, p. 81).

Whereas in the young participants only left STC, left fusiform gyrus and bilateral cerebellum were recruited in addition (Fig. 4.4, p. 73), elderly participants recruited far more brain regions during filtering (Fig. 4.7, p. 77). These additional brain regions included left lateral geniculate body, bilateral IFC, left SMA, left FEF, right PTC, left OCC, bilateral cuneus and bilateral superior colliculi. The fact that a more extensive net of co-activated brain regions was observed than in earlier fMRI studies on this matter (e.g. McNab & Klingberg, 2007) may be in part related to our testing a larger

number of participants (young: n = 40, elderly: n = 38) which increased statistical power.

With the bilateral insulae, FEF and SPC parts of the ventral and dorsal attention network described by Corbetta and Shulman (2002) were found. These are postulated to form the core of a network for frontoparietal interactions and are known to be involved in stimulus driven orienting (Corbetta *et al.*, 2008). Left SPC was activated in both age groups but regions did not exactly overlap, so that only the right SPC emerged as intersecting brain region. Also a clear right hemispheric dominance, which is characteristic for the attention networks could be observed in frontal and parietal regions in the data of the present thesis (Fig. 4.10). Those frontoparietal regions seem to play a role in attending to a location and maintaining the focus on a target which is necessary for selecting relevant among irrelevant information (Corbetta *et al.*, 2008), which was required in this task. Thereby, the FEFs that are known to control saccadic eye movements (Bruce & Goldberg, 1985; Bruce *et al.*, 1985) and play an essential role in attention mediated processes (Corbetta *et al.*, 1998; Corbetta & Shulman, 2002; Kincade *et al.*, 2005; Thompson *et al.*, 2005), might control the shift of covert attention to the target positions during the encoding phase. Whereas covert attention had to be deployed to targets in the NFHM condition as well in this study, the presence of strong distractors in the HFLM condition might have induced a stronger FEF signal. Alongside FEF, the superior colliculi are also known to play a role in the control of eye movements. They emerged during filtering in elderly only. Both structures are anatomically connected (Komatsu & Suzuki, 1985) and similar to FEF it was shown, that the superior colliculi are involved in top down as well as bottom up driven attention (Fecteau *et al.*, 2004; Sapir *et al.*, 1999).

Besides the previously discussed brain regions that were observed during filtering in both age groups, also the right OCC emerged. The exact visual areas, that were active during filtering could not be assessed during this task because retinotopic mapping was not part of this thesis. But compared to studies using this method, the activated occipital region in this thesis could embody V3 (see Wandell & Smirnakis, 2009 for

a review). The enhancement of visual areas in OCC during attention is not new to researchers on this topic and it is assumed that frontoparietal interactions are biasing this enhancement by asserting control over visual areas (Ruff, 2013). Compared to the emergence of right FEF and OCC (V3) during filtering in young, the high filtering condition elicited far more brain regions in the elderly. These are part of the visual system and involved in attention processes including lateral geniculate body, bilateral FEF, bilateral OCC (V3) and bilateral superior colliculi reflecting a stronger recruitment of brain regions with increasing age.

The observation of subcortical areas like the thalami and basal ganglia emerging during filtering is also well in line with the literature (Grill-Spector *et al.*, 2000; Baier *et al.*, 2006; Bočková *et al.*, 2011). Together with the basal ganglia the thalami are assumed to form the basis of attentional control by providing a primary filter that integrates the incoming sensory input and forwards this information to the respective cortices for further processing (Mitchell *et al.*, 2014). The basal ganglia are thereby involved in this gating mechanism by inhibiting thalamic neurons via direct connections (Frank *et al.*, 2001). In a study of McNab and Klingberg (2007) using a similar delayed matching-to-sample paradigm as it was used in this thesis, the basal ganglia (and parts of the PFC), especially the globus pallidus, were found to be activated during the preparation to filter out task relevant information. The higher the preparatory activity or "filtering set" was in participants, the less "unnecessary storage activity" was observed in right IPC.

In addition to common activated brain regions during filtering in both age cohorts, young participants recruited the fusiform gyrus among others. A subregion of this area (FFA) is known to be involved in the processing of faces (Kanwisher *et al.*, 1997). It was shown before that the fusiform gyrus is activated when face distractors are present, compared to their absence (De Fockert *et al.*, 2001). The signal in this region increased with increasing memory load. With regard to the fact that stimuli in this thesis consisted of rectangles instead of faces, it is possible that the four presented

rectangles were grouped together as a strategy to manage the task and resembled the raw scheme of a face.

The cerebellum was also among those brain regions recruited during filtering in young participants only. Researchers agree about a general involvement of the cerebellum during working memory processes alongside its role in motor control but the exact function is still not clear. An attempt to disentangle the involvement of the cerebellum during memory and filtering processes was made by Baier and colleagues (Baier *et al.*, 2014). In this study patients with cerebellar lesions, due to strokes had to perform a VWM task. Lesion patients were only impaired in performance when targets were presented among distractors compared to healthy controls. The authors attribute the cerebellum a gatekeeper role, which might be related to the basal ganglia via a corticocerebellar loop (Allen & Courchesne, 2014).

As well as in this thesis, SMA was found in other studies investigating the neural correlates of VWM and selective attention (LaBar *et al.*, 1999; Pollmann & von Cramon, 2000). During the control of movement, the SMA plays a major role (Haggard & Whitford, 2004) but its role in implicit planning of stimuli-directed actions driven by attention was also shown (Handy *et al.*, 2005).

In addition to the commonly activated brain regions in both age cohorts, elderly participants showed a much more extensive net of co-activated brain regions during filtering which might indicate that stronger filtering mechanisms are necessary in these participants. The obvious recruitment of far more regions (left lateral geniculate body, bilateral IFC, left SMA, left FEF, right PTC, left OCC, bilateral cuneus) in elderly than in young participants during cognitive tasks was also observed in several other studies (e.g. Schneider-Garces *et al.*, 2010; Geerligs *et al.*, 2014). Again, the dedifferentiation that occurred during storage of relevant information could be observed during filtering, too. The right and left OCC and the FEF were recruited instead of right only.

The effects of age observed in behavioral performance during filtering cannot be explained by neural differences with the present data. A reason for the performance

differences from a neural perspective might be a reduction in frontoparietal connections during healthy aging (Andrews-Hanna *et al.*, 2007; Damoiseaux *et al.*, 2008) leading to an impairment in prefrontal control. It is also known that posterior and frontal regions decline during healthy aging (Raz *et al.*, 2005) and several researchers support the idea that the cognitive impairments in elderly are mainly driven by a decline in prefrontal brain regions (Raz & Rodrigue, 2006; Lindenberger *et al.*, 2013). In other studies increased frontal activations in elderly were reported (e.g. Payer *et al.*, 2006), which could not be observed here. This often reported increase in prefrontal activity is explained as a mechanism to compensate with dedifferentiation that occurs during aging. Based on the reviewed studies, it can be assumed that top down control was slightly impaired in the elderly participants of this study. However, these theories are speculative based on the present data.

Alongside dedifferentiation during healthy aging, a shift of recruited brain regions during different cognitive tasks can be observed along an anterior posterior axis (Davis *et al.*, 2008). Whereas frontal parts of the brain are often stronger activated in elderly in comparison to young participants, this effect is reversed in posterior parts of the brain and often reflected in an increase in performance (e.g.Gutchess *et al.*, 2005; Payer *et al.*, 2006; Davis *et al.*, 2008). This directionality of compensational mechanisms described in the literature could not be observed in this study. Whereas elderly indeed recruited more parts of the frontal brain in contrast to young participants more posterior parts of the brain like cuneus, pTC and bilateral OCC were recruited as well. In addition to the behavioral and neural measurements of memory and attention processes, structural measures of the dopaminergic innervated substantia nigra and the cholinergic innervated basal forebrain were assessed and analyzed with regard to behavioral performance. The background of assessing volumes and MT ratio from those structures is the neural decline occurring during healthy aging. Therefore, stronger effects were expected to occur in the elderly cohort. However, an association between SN_{vol} and memory deficit was found in young participants but not in the elderly. Participants with a higher SN_{vol} showed a lower memory deficit in the combined task.

Due to the dopaminergic innervation of the substantia nigra these results suggest that memory processes are modulated by dopamine. Associations with SN_{vol} were not found in the performance of the elderly, although a higher SN_{MT} was found to be associated with lower hit rates and correct rejections in the LFLM condition. If macromolecules were the main drive behind the magnetization transfer, high MT ratio would reflect a higher presence of macromolecules in substantia nigra. Intuitively, a high amount of macromolecules in a cell reflects a healthy state. However, certain diseases are accompanied by the accumulation of large macromolecules in a neuron (e.g. AD). Hence, the higher MT ratio associated with an impairment in filtering could point to a possible unhealthy state of neurons in the substantia nigra. With the absence of a significant association with SN_{MT} in the HFLM condition, the results are more difficult to interpret and further research has to be done on MT ratio measures to draw conclusions from this structural measure.

In general, the present results show that elderly need to recruit more brain regions in order to meet the task demands. This finding is in line with the compensation-related utilization of neural circuits hypothesis (CRUNCH) postulating a compensational mechanism that becomes necessary becaus of the neural decline during healthy aging (Reuter-Lorenz & Cappell, 2008). Whereas certain brain regions are overactivated or bilateralized during low task demands this compensational mechanism is fully utilized during high task demands leading to underactivation in comparison to young participants.

5.2 Influence of working memory capacity on memory and filter correlates

In several studies, strong differences in VWM capacity between individuals and disease groups (e.g. Schizophrenia) were observed (e.g. Daneman & Carpenter, 1980; Engle *et al.*, 1999; Fukuda *et al.*, 2010). Machizawa and Vogel (2004) were the first to propose that this variation stems largely from individual differences in distractibility

rather than differences in VWM capacity per se. In this thesis, the individual VWM capacity was calculated from performance measures in a separate test to investigate the relationship between individual capacity limits and distractibility. Similar to the findings in other studies (e.g. Todd & Marois, 2004), VWM capacity increased with an increasing number of items that had to be memorized but reached a plateau in the younger participants or even dropped in elderly respectively (Fig. 4.15, p. 87). The drop might reflect a VWM capacity limit of three to four items which is in line with the literature (Cowan, 2010). The further increase on the other hand might reflect a change in strategy. When VWM capacity is reached participants might start chunking stimuli together to memorize patterns instead of single items (Cowan, 2010).

The overall performance was lower in elderly in comparison to young participants for all presented sets except set size two. To investigate whether elderly participants with a high VWM capacity were as good as young participants with a low VWM capacity, the median of set size two to four was calculated and each age group was divided by a median split. The results revealed no difference in performance between young low and elderly high performer, suggesting that VWM capacity seems to be vulnerable to age but individual differences are not. Again these findings are supported by similar findings in the literature (Matsuyoshi *et al.*, 2014).

In terms of the combined task individual VWM capacity was expected to be correlated with direct and indirect behavioral measures of memory performance. Indeed a higher individual VWM capacity in young was found to be related with better performance in hit rates (NFHM) and faster responses (LFLM, HFLM; Fig. 4.16, p. 90). In elderly associations between VWM capacity and responses with regard to hit rates were found across all conditions too. However, higher VWM capacity was reflected in slower responses in contrast to young participants (Fig. 4.17, p. 91). Hence, VWM capacity seems to have an impact on memory processes regardless of the presence or absence of distractors. The opposite effect on responses in elderly might reflect a change in strategy with increasing age to compensate for age related impairments. A so called speed/accuracy trade-off might be the consequence resulting in taking more

time to accurately perform the task. In a study from the late 70s, it was shown that elderly participants gather information before making a decision to avoid mistakes (Rabbitt, 1979). However, it seems that this strategy was used by elderly participants with a higher VWM capacity only. In addition to the general influence of VWM capacity on hit rates in both age cohorts, a higher VWM capacity was associated with lower memory deficits in young. This effect was expected and endorses this indirect behavioral measure as a good mirror of memory performance. Alongside associations with measures of memory performance, VWM capacity was associated with faster responses in the correct rejection of the strong distractor in young.

In addition to correlations with memory performance, effects of VWM capacity on filtering performance were found. Young participants with a high VWM capacity responded faster when the strong distractor was probed than participants with a low VWM capacity. These results support the findings of Vogel and colleagues (2004; 2005), showing that increased distractibility is reflected in lower VWM capacity. The lack of an interaction between VWM capacity and filtering ability in elderly might point to a different strategy to compensate for the impaired VWM capacity during healthy aging. However, a trend towards a significant correlation was found in elderly between VWM capacity and correct rejections in the high filtering condition.

By looking at effective storage activity (and filter activity) with regard to individual differences in VWM the link between distractibility and VWM capacity was expected to to be reflected in corresponding activity changes in memory load dependent brain regions, especially PC, as it was found in other studies (Todd & Marois, 2004, 2005; Xu & Chun, 2005; McNab & Klingberg, 2007). This was not the case: no significant correlations of VWM capacity with effective storage activity in IPC were observed in any of the analyzed age groups. Instead, higher effective storage activity was found in elderly participants with a higher VWM capacity in left STC (Fig. 4.19, p. 92). The involvement of - mostly medial - TC in working memory was reported before, but its exact role remains unknown (Olson *et al.*, 2006; Jeneson & Squire, 2012). In a study investigating the neural substrates of VWM capacity differences, STC was found to be

involved in a listening span test. Beyond the mentioned studies, associations between working memory capacity and STC were not yet reported.

By means of calculating VWM capacity from a separate task instead of the fMRI task, the often made pitfall of circular analysis was avoided in this thesis. Furthermore, the fact that this separate assessed VWM capacity was correlated with behavioral measures of memory performance in the fMRI task makes this VWM capacity a strong index of memory performance. In other studies, showing a reflection of VWM capacity in BOLD response mostly in IPC, the VWM capacity was calculated from the same task during which BOLD responses were assessed (Todd & Marois, 2004, 2005; Xu & Chun, 2005; McNab & Klingberg, 2007). Moreover, whereas in the study of Todd and Marois (2004) VWM capacity measures were averaged across the whole group and compared with IPC responses, other researchers used the individual VWM capacity for correlation analysis (Xu & Chun, 2005). In support to the present results, recent studies did not find correlations between VWM capacity and load sensitive brain regions (Magen *et al.*, 2009; Matsuyoshi *et al.*, 2012). In a study of Magen and colleagues (2009) three experiments were conducted, consisting of a classical delayed matching-to-sample task with a varying delay interval. VWM capacity increased with increasing set size but reached a plateau between set size three and five. Interestingly, BOLD activity in the previously defined load sensitive PC increased beyond the performance level with increasing set size during longer delay intervals. The authors concluded that activity in PC reflects attentional demands rather than a concrete VWM capacity limit, which is supported by the previous reported interaction between parietal activity and performance in correct rejections.

Despite the lack of significant associations between VWM capacity and parietal activity in any of the age groups, several interactions between filter activity and VWM capacity were found in both age cohorts. In young participants filter activity in the left basal ganglia (pallidum) was increased with increasing VWM capacity (Fig. 4.18, p. 92). A similar association was found by McNab and Klingberg (2007). VWM capacity was correlated with left basal ganglia (putamen/ pallidum) as well, but this

region was defined in the cue phase rather than in the encoding phase. The activity found in basal ganglia was reported as "filtering set activity" that emerged whenever a distractor was cued in contrast to cues after which only targets followed. Filtering set activity was indeed predictive of successful filtering of distractors, however, this was only indirectly measured. The results might explain individual differences in VWM capacity to some extend as they show the basal ganglia, which are involved in filtering possibly as a gate keeper, are recruited differently, depending on the individual VWM capacity. This idea is further supported by the previously discussed association between individual VWM capacity and response times in correct rejections.

Although basal ganglia were found to be recruited during filtering as well in elderly, filter activity in these regions was not correlated with VWM capacity. Instead capacity was associated with filter activity in the left thalamus and cuneus (Fig. 4.19, p. 92). The thalamus has been proposed to be involved in the gating mechanisms described before (Baier *et al.*, 2006), by being inhibited via direct connections from the basal ganglia (Frank *et al.*, 2001). The association found here still supports the idea of an interaction between individual filtering mechanisms and VWM capacity.

Filter activity also increased in cuneus with increasing VWM capacity in the elderly. This structure is mainly known to be involved in visual processing in general. Together with the present results, it seems that visual areas are enhanced in elderly via attentional modulation required by the task at hand. The degree of this modulation is depending on limited resources, reflected in an association with VWM capacity. Mayer and colleagues (Mayer *et al.*, 2007) investigated shared neural correlates of VWM and attention and found the cuneus to be activated amongst others.

Other than the behavioral and functional results, the structural parameters that should reflect underlying structural correlates of memory and filtering processes were not associated with individual VWM capacity. This suggests that the individual differences of this measure are either dependent on other structural brain regions or are solely dependent on functional processes. It is also likely that the used VWM capacity test is not sensitive enough to track changes dependent on structural differences.

However, the findings of previously discussed studies in combination with the lack of a correlation between memory load dependent brain activity and VWM capacity in this thesis are in conflict with the idea of a certain brain region that underlies a concrete item limit. The present results rather point to the concept of shared limited resources that are defined by task demands. Despite the missing relation between memory load dependent brain activity and VWM capacity, a correlation between individual memory limits measured in a separate task and filtering performance in a high demanding attention task was shown, supporting the findings of Vogel and colleagues (Vogel & Machizawa, 2004; Vogel *et al.*, 2005). However, the hierarchy of this relationship remains unknown. The question whether good filtering strategies lead to higher VWM capacities or whether higher capacities are a necessary requirement for a good filtering ability cannot be answered in this thesis.

5.3 Influence of drug administration on memory and filter correlates

Recent lesion and pharmacological studies suggest a strong role of dopamine during VWM processes (Chao & Knight, 1995; Durstewitz *et al.*, 2000; Seamans & Yang, 2004; Cools *et al.*, 2007), whereas acetylcholine seems to be involved in the modulation of filter processes (Thiel *et al.*, 2005; Furey *et al.*, 2007) but the exact role of these neurotransmitters is still unknown. Paradoxically, memory deficits occurring in patients suffering from AD are treated with acetylcholine level increasing drugs. In a study of Furey and colleagues (2000) an increased acetylcholine level, that was pharmacologically induced, was leading to a better VWM performance. This effect was accompanied by a higher neural selectivity in extra striate cortex and a reduced recruitment of prefrontal brain regions during the task. The authors concluded that the increased acetylcholine level reduced processing demands in the brain and therefore reduced prefrontal activity. The fact that frontal brain regions, which are known to be involved in attentional filtering, are strongly modulated by dopamine, together

with the previous mentioned studies, challenge the idea of a concrete involvement of dopamine during VWM processes and acetylcholine during attentional processes only. Beyond behavioral and neural measures of VWM and selective attention, the role of the neurotransmitters dopamine and acetylcholine during these cognitive processes was investigated in this thesis by pharmacological modulation. Oral administration of levodopa, which is a precursor to dopamine and able to cross the blood brain barrier, had no effect on behavioral and neural correlates of working memory and filtering in young and elderly participants (Fig. 4.20, p. 95). Similarly, oral administration of galantamine which increases the acetylcholine level by blocking the cholineesterase had no effect on behavioral correlates. The lack of drug effects was expected in younger participants but not in the elderly.

The effect of dopamine on cognition during aging can be described by an inverted U-function, which describes different individual baseline levels of dopamine (Cools & D'Esposito, 2011; Störmer *et al.*, 2012). Good VWM performance seems to be dependent on an optimal dopamine level. A decrease or an increase of the dopaminergic baseline level in the brain beyond the optimum seems to impair VWM performance. During healthy aging a loss of dopaminergic receptors and, therefore, a decreased dopaminergic modulation can be observed (Bäckman *et al.*, 2006; Li *et al.*, 2010). This leads to a shift of dopaminergic effects beyond the optimum. It was therefore expected that young participants dopamine level would be shifted slightly over the peak of the U-function after drug modulation from the optimal dopaminergic baseline to a suboptimal level, leading to a decrease in performance. Similarly, levodopa administration in elderly should have led to an improvement to a "normal" dopaminergic level reflected in an improvement in performance after administration. With regard to the absence of any significant effects of drug administration in the behavioral results it is conceivable that the individual baseline level of dopamine was indeed shifted in the expected way but on a small scale, not leading to any behavioral changes. The exact individual baseline level of the tested neurotransmitters in the brain could not be measured because of ethic and methodological reasons. For future studies on dopaminergic

effects on cognitive functions it would be inevitable to measure dopaminergic baseline levels in the brain. At the moment only one non-invasive method is available for humans which is PET imaging.

The lack of dopaminergic effects on behavioral performance in this thesis might be due to other reasons as well. In several studies it was shown, that the effect of dopaminergic modulation on task performance is dependent on the VWM capacity, which in turn seems to rely on individually different dopamine baseline levels (Kimberg *et al.*, 1997; Mattay *et al.*, 2000; Cools *et al.*, 2008). Whereas participants with a low VWM capacity benefited from pharmacological dopamine enhancement, high VWM capacity participants were impaired in VWM performance. This finding supports the idea of VWM performance being based on different dopamine baseline levels, reflected in the inverse U-function. It is assumable that individuals with a low VWM capacity, which is accompanied by a low dopamine level, improve performance after dopaminergic enhancement due to a shift on the function to the optimum, whereas dopaminergic level of high VWM capacity performer was shifted over the optimum. To test whether this was the case in this thesis, participants of each drug group were separated into two groups by VWM capacity median split. Performance in the combined task was then reanalyzed by taking the neurotransmitter enhancement in each group into account. By testing for drug effects in high and low VWM capacity groups separately, no effect of levodopa (or galantamine) was found (Tab. 4.8, p. 98). Against the background of different dopaminergic baseline levels in participants with a low or high VWM capacity, it is assumable that the baseline level difference between young and elderly was big enough to show differences in VWM capacity. However, this baseline level in both age groups might have been still within the optimum in a way, that an increase in dopamine via pharmacological modulation was leading to a slight shift at the peak of the U-function only.

In line with the results of this thesis, a lack of an effect of levodopa in elderly participants was observed in an fMRI study of Onur and colleagues (Onur *et al.*, 2011). Young and elderly participants had to perform a modified Stroop task testing inter-

ference effects, after levodopa had been administered to all participants. Similar to the results in this thesis, no effects of levodopa on behavioral performance were found. The authors also explained the lacking effects with optimal baseline levels of dopamine in elderly. In the discussed study of Onur the same single dose of levodopa (100 mg levodopa, 25 mg carbidopa) was used as it was the case in this study. It is also possible that the used doses of levodopa were too small to modulate the baseline level in such a strong way that this shift has an effect on behavioral measures in young participants. In clinical treatment of PD higher doses of levodopa are used, e.g. 250 mg. However, higher doses are accompanied by stronger side effects such as nausea. Therefore, in addition to higher levodopa doses, additional drugs reducing side effects are administered in patients suffering from PD.

Alongside effects of drug modulation on behavioral performance, effects on hemodynamic response during memory and filtering processes were assessed. Effects of dopaminergic and cholinergic drug modulation were found in neural correlates of filtering in young participants only. No effects on memory correlates were observed in both age groups. Filter activity in right SPC and bilateral cerebellum was decreased after dopaminergic administration (Fig. 4.21, p. 99), suggesting a lower need for a recruitment of these brain regions. The cerebellum with its function in motor control plays an important role in PD, which is characterized by a degeneration of dopaminergic neurons. Studies reporting effects of levodopa on cerebellar function are sparse but it was shown, that functional connectivity in the cerebellum (and brainstem) only was influenced by dopaminergic medication in PD patients (Jech *et al.*, 2013). The authors interpreted the increase in connectivity after medication as a normalized state, whereas connectivity in PD patients seems to be abnormally attenuated. In another study it was shown that connectivity between basal ganglia and cerebellum is impaired in patients suffering from PD (Wu *et al.*, 2012). The dopaminergic effects on filter activity in this thesis are supported by the previous mentioned study of Baier and colleagues (Baier *et al.*, 2014). They interpreted impairments during filtering resulting from cerebellar lesions as impairment in the gate keeper network. The results point

to a clear involvement of dopamine in filtering processes. Likely, these processes are driven via basal ganglia and they challenge the idea that dopamine is only involved in in memory processes.

In addition to the cerebellum, filter activity was also attenuated in right SPC after dopaminergic as well as after cholinergic modulation (Fig. 4.21, p. 99; Fig. 4.22, p. 100). Dopaminergic neurons are not abundant in parietal brain regions and, therefore, it is likely that the parietal modulation was driven by frontoparietal interactions. The SPC is part of the dorsal attention network proposed by Corbetta and Shulman (2002) and was therefore postulated to be involved in top down control of visual attention. Hence, a reduction of filter activity after drug modulation can be interpreted as a decreased need for the recruitment of parietal areas during the filtering of irrelevant information. The same mechanisms might be true for the cholinergic effect on right SPC whereby in contrast to the indirect effect dopamine can assert on SPC only, cholinergic neurons are present in this brain region. Furthermore, the role of acetylcholine during attentional processes was expected because of the current findings reported in the literature (Thiel *et al.*, 2005; Furey *et al.*, 2007). The attenuation of filter activity after galantamine administration, that was found alongside the right SPC in the left STC as well (Fig. 4.22, p. 100), can be interpreted again as a lower necessity for a recruitment of those brain regions. However, the effect of galantamine administration on filter activity in STC was unexpected because of the well-known role of the TC in memory processes (Jeneson & Squire, 2012; Olson *et al.*, 2006). It is conceivable that STC is modulated by cholinergically innervated parietal brain regions, but based on the present data this remains speculative.

In contrast to the previously described brain regions, filter activity in fusiform gyrus was increased after cholinergic modulation in young participants (Fig. 4.22, p. 100). It was previously discussed, that the engagement of fusiform gyrus during filtering might reflect a strategy of chunking stimuli to face like objects instead of memorizing each stimulus on its own. With regard to the fact that acetylcholine is well-known to be involved in the attentional driven enhancement of visual areas (Bauer *et al.*,

2012; Ricciardi *et al.*, 2013), cholinergic stimulation in this thesis might have led to an enhancement of fusiform gyrus activity due to the attentionally high demanding task. Moreover, enhancement of fusiform hemodynamic response via cholinergic modulation was reported before by other researchers (Furey *et al.*, 2000; Bentley *et al.*, 2003, 2009). Another matter that one has to keep in mind when looking at pharmacological effects on behavioral performance is the individual difference in structural innervation. An attempt to account for this issue was made in this thesis by assessing MT ratio and volumes of the dopaminergic innervated basal ganglia and cholinergic innervated basal forebrain. Effects of dopaminergic modulation on behavioral performance was therefore expected to occur in dependency on SN_{MT} and SN_{vol} whereas cholinergic effects were expected to be driven by differences in BF_{vol}. However, no effects of levodopa administration were found in any of the age cohorts with regard to structural attributes. The same reasons that were discussed before regarding the missing effects of levodopa administration might be responsible for the lack of effects in terms of structural measures.

In terms of galantamine, expectations were fulfilled to some extent. First, associations between galantamine administration and basal forebrain measures were found in the elderly only, which was expected because of the decreased neurotransmitter level associated with healthy aging. Second, administration of this drug was leading to a higher filter deficits in participants with a lower BF_{vol}, whereas filter deficit decreased in participants with a low volume (Fig. 4.24, p. 103). The results show, that an intact basal forebrain seems to be necessary during choline modulated filtering. Lesions in the basal forebrain can lead to attentional deficits, which is known from animal studies as well(Voytko *et al.*, 1994; Turchi & Sarter, 1997). Furthermore, AD is characterized by a degeneration of neurons in the basal forebrain leading to cholinergic depletion in the brain. Together, these results show a link between cholinergic modulation and filtering performance via BF_{vol}.

Galantamine was although found to be associated with filtering in terms of response times in correct rejections of both filtering conditions in dependency on SN_{vol} (Fig.

4.23, p. 102). This association between galantamine administration and substantia nigra measures was unexpected based on the known dopaminergic innervation. Furthermore, this effect was found in young participants only. Only those participants responded faster when the distractor was probed after galantamine administration, whose substantia nigra was found to be small. The interaction of cholinergic and dopaminergic neurons in the basal ganglia is known from PD. The movement impairment in PD was attributed to imbalance between acetylcholine and dopamine levels in the basal ganglia (Clarke, 2004; Calabresi *et al.*, 2006). With the degeneration of dopaminergic neurons the input on the basal ganglia is reduced leading to an overactivation of cholinergic neurons. Moreover, it was shown that acetylcholine modulating drugs can improve cognitive performance in PD patients (Emre *et al.*, 2004). It is likely that administration of galantamine was leading to an imbalance of neurotransmitters, leading to differences in response times in the filtering conditions.

An effect of galantamine in releation to SN_{MT} was found in elderly in the high memory condition (Fig. 4.24, p. 103). Elderly participants improved performance after galantamine administration based on a high SN_{MT}. As mentioned before, a higher SN_{MT} can be interpreted as the presence of more macromolecules in that area. Reduced SN_{MT} was found in PD patients for example (Eckert *et al.*, 2004; Seppi & Schocke, 2005), leading to the assumption that lower SN_{MT} reflects a degeneration of dopaminergic neurons. An imbalance of dopamine and acetylcholine in the basal ganglia might also be the reason for the effect of galantamine in dependency on SN_{MT}.

Together, the present findings show that the involvement of dopamine in memory processes and acetylcholine in attentional processes and underlying neural correlates only is over simplified. Effects of pharmacological modulation in this study are rather depending on several factors such as neurotransmitter baseline levels and structural integrity. These factors again seem to be highly dependent on age, reflected in different results across both age cohorts. It is likely that the effect of galantamine on filter deficit (in dependency on BF_{vol}) was only seen in elderly because of the presence of neurotransmitter deficits, which might not have been the case in the young partici-

pants. Furthermore, galantamine and levodopa had no significant effect on behavioral performance in both age cohorts and on functional correlates in elderly. Whereas a function, describing the relation between acetylcholine and cognitive performance is not known yet, it can be assumed that the reasons for a lacking effect of galantamine on behavioral performance and brain activity have similar reasons as the lacking effect of levodopa. Neural substrates of cholinergic systems in the brain are highly influenced by aging (Dewey *et al.*, 1990; Mitsis *et al.*, 2009; Schliebs & Arendt, 2011) and this degeneration is known to affect cognitive performance (Bartus, 2000). On the one hand it is conceivable, that the lack of a galantamine effect is due to the use of a too low dose of galantamine (8 mg). Higher doses were not used in this thesis because of an increasing risk of side effects with increasing dose. On the other hand, it is also likely that the used paradigm was not sensitive enough to expose differences induced by the drug. Furthermore, it is known that some PD patients are not responding to levodopa (Lledo *et al.*, 2000; Kavanagh *et al.*, 2011). It is also known that neurotransmitter modulating drugs are dose dependent with regard to the individual body weight (Arabia *et al.*, 2002; Knecht *et al.*, 2004). To test dose-dependent effects, statistical tests on behavioral, functional and structural measures were repeated with body weight as covariate. No significant interactions between body weight and drug administration were found ($p > .05$), so that it can be ruled out that drug effects were modulated by body weight in this study.

For further studies, one possibility might be to include participants that are older than participants of this thesis were. It is known that $5 - 10\%$ of dopaminergic receptors in the basal ganglia get lost per age decade (Bäckman *et al.*, 2006) and it is assumable that this is true for more brain regions. That suggests that dopaminergic drugs can have stronger effects or induce stronger shifts in terms of the U-function depending on the age decade. Because neurotransmitter levels in the brain could not be measured in this thesis because of ethical and methodological reasons, the supposed reasons for the lacking effects of dopaminergic and cholinergic enhancement cannot be tested. For

future studies a good compromise would be to measure individual neurotransmitter baseline levels via PET.

5.4 Influence of genetic diversity on memory and filter correlates

In the previous section, the effects of dopamine and acetylcholine levels modulating drugs on behavioral and neural correlates of working memory and selective attention were discussed. The results were interpreted with regard to different baseline levels of the neurotransmitters under investigation, although the actual individual baseline levels in the brain could not be measured. An attempt to get a better idea of individual differences was made by identifying naturally occurring variants of genes that are known to be involved in the metabolic pathways of dopamine and acetylcholine.
Polymorphisms that are known to be involved in memory processes are variations in the COMT ($Val^{158}Met$) and DBH gene ($G^{444}A$). Enzymatic activity of the catechol-o-methyltranferase is clearly higher in G-allele carriers compared to A-allele carriers leading to a higher degree of dopaminergic degradation. The DBH gene codes for the dopamine degrading and norepinephrine producing enzyme dopamine-ß-hydroxylase. The A-allele is associated with a lower enzymatic activity of DBH leading to a lesser degree of dopaminergic break down. Because a higher enzymatic activity is associated with a higher emergence of norepinephrine, this neurotransmitter has also to be taken into account when interpreting effects of the DBH polymorphism.
In several studies differences in VWM tasks were found based on COMT (Egan *et al.*, 2001; Mattay *et al.*, 2003; Apud *et al.*, 2006; Clark & Noudoost, 2014) or DBH polymorphisms (Parasuraman *et al.*, 2005; Greenwood *et al.*, 2009b). However, in the present thesis no significant effects of COMT polymorphism on behavioral and neural correlates of working memory and selective attention were found in any of the tested age cohorts. In addition to COMT and DBH, the gene polymorphism CHRNA4 was identified for each participant which plays a role in cholinergic transmission in the

brain. Also this gene polymorphism was not found to be associated with behavioral performance in the combined task. One reason for the negative findings could be a to small sample size. The smallest polymorphism group in the young and elderly cohort consisted of six participants only, which might be a too small number to reveal effects of gene polymorphisms. It is also likely that other polymorphisms (e.g. in DAT1, DRD2, CHRFAM7A or CHRM4 gene), that are involved in the dopaminergic and cholinergic pathway play a stronger role in the required processes or that rather a pattern of different polymorphisms has to be assessed to observe significant effects. We focused on COMT, DBH and CHRNA4 only, because of the reported interactions with memory and attention performance.

However, independent of behavioral results, effects of one gene polymorphism were indeed found with regard to hemodynamic responses. The CHRNA4 gene is coding for the $\alpha 4$ subunit of the nicotinic $\alpha_4\beta_2$ receptor. The exact impact of the naturally occurring cytosine (C) to thymine (T) substitution on that gene is not known but variants of these polymorphisms were reported to be related to performance in attention tasks (Parasuraman *et al.*, 2005; Greenwood *et al.*, 2009a; Reinvang *et al.*, 2009; Espeseth *et al.*, 2010; Greenwood *et al.*, 2012). Effective storage activity was found to differ significantly between elderly CHRNA4 polymorphisms carriers (Fig. 4.25, p. 108). The T-allele was associated with a lower effective storage activity in left aIPC. Effects of CHRNA4 polymorphisms were expected to occur in this brain area among others because of the high degree of CHRNA4 expression in frontal cortex and PC as well as in the thalami (Léna & Changeux, 1998; Gotti *et al.*, 2006). The fact, that different genetic CHRNA4 backgrounds were associated with attention performance in other studies is not in conflict to the association of the polymorphisms with the more storage related aIPC activity found here, because of the reported interaction between parietal activity and filtering ability. It is very likely that the intersection between memory and attentional processes reflected in parietal activity, is modulated by acetylcholine and therefore based on the individual genetic background. The present results are supported by a study of Winterer and colleagues (Winterer *et al.*, 2007)

who investigated the neural genotype effects of CHRNA4 by means of a visual oddball task, which was highly depending on attentional processes. The task elicited the classical attention network in the tested sample, but a gene dose effect of CHRNA4 polymorphisms was only found in left IPC in young participants with TT allele carriers showing the strongest hemodynamic response during the task.

Alongside the reported effect in the elderly, an association between CHRNA4 polymorphisms and BF_{vol} was found in the young cohort (Fig. 4.26, p. 109). In T-allele carriers a higher volume was observed. It was shown before that neurons of the basal forebrain in the rat have a high degree of $\alpha_4\beta_2$ receptor expression (Azam *et al.*, 2003). Moreover, the major cholinergic input to the cortex has its source in the nucleus basalis Meynert, a part of the basal forebrain (Perry *et al.*, 1999) and therefore it is likely that CHRNA4 expression is related to the individual BF_{vol}.

Young and elderly participants showed different polymorphism effects. This might reflect, that aging influences the neurotransmitter requirement, necessitating different neurotransmitter level demands in young and elderly participants. Also as only the function of the CHRNA4 polymorphism is unknown, an association between acetylcholine and the discussed correlates can be assumed without further conclusions drawn on certain acetylcholine levels. On a molecular level the polymorphisms might have pretranslational effects by expressing destabilized RNA (Ribonucleic acid) or posttranslational effects by influencing RNA folding, leading to a change in receptor function but the exact mechanism remains unknown.

To conclude, the present results show that individual phenotypes should be taken into account when interpreting behavioral and neural correlates in terms of underlying neurotransmitter levels. For further studies on that topic, it would be inevitable to include larger sample sizes to maximize statistical power. It would also be more informative to look at several gene patterns and possible gene-gene interactions. In this thesis, no gene-gene interactions were assessed because of the small sample size. However, despite the small sample size associations between acetylcholine modulating gene variants and neural correlates of attention processes were found. Furthermore, by

looking at CHRNA4 polymorphism variants, a possible neurobiological determinant of the interaction between working memory and selective attention processes in IPC was found.

5.5 Summary

Increased memory and attentional demands in the paradigm tested in this thesis resulted in worse performance across all age groups. Elderly participants showed lower hit rates during filtering but not during the correct rejection of distractors. The present findings reject the hypothesis of a general deficit in filtering associated with healthy aging. In the fMRI data, contrasting conditions with a high memory (no filtering) and a low memory (high filtering) load, the IPC emerged in both age cohorts. Filtering ability, as reflected in the correct rejection of a distractor, was associated with effective storage activity in IPC in young and elderly participants, reflecting a successful suppression of task irrelevant information. The present results provide new insight into the interplay between memory and attention processes, reflected in hemodynamic response differences in IPC. The inverse contrast revealed a network of co-activated brain regions associated with the filtering of information. Common filtering associated activity across both age cohorts was found in bilateral insulae, bilateral thalami, bilateral basal gangliae (striatum/ caudate ncl.), right MFC, right OCC and right SPC. The recruitment of a greater number of brain regions during filtering in elderly relative to young participants might reflect compensatory mechanisms that become necessary due to neural degeneration occurring during healthy aging and related cognitive impairments. With regard to brain volume, the substantia nigra volume was found to predict memory deficits in young participants only. Despite its role in acetylcholine generation, basal forebrain measures were not related to memory or attention performance in either age cohort.

Individual differences in filtering were suggested to be related to differences in VWM capacity (Vogel & Machizawa, 2004). In the present thesis the proposed relationship

between filtering ability and VWM capacity was also examined using a non-circular test of VWM capacity outside the MR scanner. Marked differences were found between VWM capacity across and in between age cohorts. Elderly participants with a high VWM capacity performed as good as young participants with a low VWM performance, leading to the assumption that inter individual VWM capacity differences are as large as the effects on aging on VWM capacity. With regard to performance in the memory and filter task, a high VWM capacity was reflected in higher accuracy or faster response times in young. In contrast, elderly participants with a high VWM capacity showed the slowest hit responses, suggesting that the elderly may use a different strategy. In addition to these results, VWM capacity was predictive of memory deficits in young. Furthermore, a lower VWM capacity was associated with increased distractibility in the high filtering condition, supporting the findings of other researchers on this topic (Vogel & Machizawa, 2004; Vogel *et al.*, 2005). In terms of neural correlates, the predicted association between the previous defined IPC as an interaction node between memory and filtering processes and VWM capacity was not found. Instead, storage-related activity differences were reflected in VWM capacity in STC in elderly. Furthermore, VWM capacity was associated with filter activity in the basal ganglia (pallidum) in the young participants and with thalamus and cuneus in the elderly. The association between VWM capacity and brain regions described as classical gatekeeper network (Baier *et al.*, 2014) further point to the notion that individual filtering and memory differences are intertwined and based on neural differences. The present results are contrary to the idea of activity in a certain brain region reflecting a concrete item limit. As the measured interactions between filtering and memory correlates do not reveal causal dependencies, inferences about the hierarchical relationship between both processes cannot be made based on the present data.

Effects of neuromodulation in terms of acetylcholine and dopamine revealed ambiguous results in the different age cohorts. In both age cohorts no effects of dopaminergic modulation on behavioral or structural measures were found. On a neural level, reduced filter activity was observed in the right SPC and bilateral cerebellum after

levodopa administration in young. By assuming performance followed an inverted U-function of dopamine baseline level, levodopa administration might have caused a small change in dopamine levels, but did not result in behavioral effects or effects that were not with the paradigm used here. However, the effects of levodopa on the brain activity associated with filteringpoint to an involvement of dopamine in filtering processes possibly via interactions between the cerebellum and the basal ganglia.
Pharmacological modulation of the acetylcholine level had no impact on behavioral performance in the combined task in any of the age groups. Similar to levodopa administration no effects of galantamine were observed on neural correlates in the elderly. However, administration of galantamine was leading to decreased filter activity in right SPC, left STC and increased activity in fusiform gyrus in the young. Whereas a galantamine effect during filtering was expected in parietal and visual areas due to the cholinergic innervation of the respective brain regions, modulation of filter activity in STC was not expected. This effect might have been driven via parietal modulation of temporal areas. Further relations between galantamine administration and correlates of filtering were found in terms of structural data. Pharmacological cholinergic modulation was leading to a higher filter deficit only in elderly participants with a low BF_{vol}. With regard to AD, which is characterized by a degeneration of cholinergic neurons in the basal forebrain, the link between structural facility and behavioral performance poses an important step to better understand how pharmacological therapies impact behavior. A similar effect, as the one previously reported, was found with galantamine in dependency on SN_{vol} in young participants. Only those participants whose substantia nigra was found to be small responded faster on correct rejections after galantamine administration. The results point to the possibility of a certain ratio between dopamine and acetylcholine in the basal ganglia as being necessary for a good filtering performance. This idea is supported by the fact that acetylcholine modulating drugs improve cognitive performance in patients suffering from PD (Emre *et al.*, 2004). In elderly participants galantamine had an effect on memory performance depending on structural integrity of the substantia nigra (SN_{MT}). Together the results

show that the previously reported interaction of memory and filtering processes can also be observed on a pharmacological level where levodopa and galantamine both have an impact on neural correlates of filtering and memory.

A neurotransmitter modulated interaction between memory and attention processes is further supported by considering the genetics of the participants. No differences in behavioral, structural or functional correlates were found in participants with variants of the dopamine associated COMT or DBH polymorphism. However, the CHRNA4 polymorphism, which is known to be associated with the function of a nicotinic receptor, was related to memory driven hemodynamic response in left aIPC in elderly, pointing to an interaction between memory and filtering processes. Furthermore, variants of the CHRNA4 polymorphisms were reflected in different BF_{vol} in young participants, showing the importance of considering both genetic and structural information into account when interpreting data related to neurotransmitters.

To conclude, the results of the present thesis provide evidence for the interaction between working memory and filtering processes. Postulated correlates of memory processes such as an association between memory deficit and effective storage activity, SN_{vol} or VWM capacity in young and/ or elderly were found in this thesis. In addition hypothesized correlates of attention processes such as associations between galantamine administration and filter activity in parietal and visual brain regions, between galantamine and filter deficit in dependency on BF_{vol} or between the latter and CHRNA4 polymorphisms were found. However, hints of a strong interaction between memory and attention processes come from several interaction effects such as the association between effective storage activity and correct rejections in IPC, associations between VWM capacity and correct rejections or filter activity in subcortical (thalamus, basal ganglia) and visual areas (cuneus). Furthermore, interactions between levodopa administration and effects on filter activity (cerebellum, SPC) or between galantamine administration and correct rejections in dependency on SN_{vol} as well as associations between galantamine and hits in dependency on SN_{MT} or between CHRNA4 polymorphisms and effective storage activity in IPC support the roles of

the neurotransmitters dopamine and acetylcholine during this interaction. As a neural substrate for this interaction, the IPC seems to be a main node by processing relevant as well as irrelevant information as such. The effects of neurotransmitter modulation on such processes found in this thesis on a neural level only were likely based on different baseline levels depending on age but also on structural as well as genetic factors. The paradoxical effect of cholinergic treatment on memory performance (Furey *et al.*, 2000) and cognitive performance in PD patients can be better understood by taking the interaction between behavioral and neural correlates of memory and filtering into account. A better understanding of this interplay and the effects of pharmacological neurotransmitter modulation is necessary to guide the development of new treatment strategies.

6 Study limitations

Although the present results have been discussed with regard to possible neurobiological mechanisms, it is important also to address methodological issues that also may have influenced the results. First of all, the sample size may have been too small to reveal stringer effects of medication or genetics. To cope with the small sample size, data of placebo groups were collapsed over the different age groups for all analyses to increase statistical power. Furthermore, an additional number of participants were scanned using the same paradigm but without drug administration to increase sample size for a reanalysis of genetic data. However, these data cannot yet be presented in this thesis. One reason for the small sample size was the low availability of elderly participants that were appropriate for the study because of the strict exclusion and inclusion criteria. Moreover, as a requirement from the local fMRI management a medical doctor had to be present in every fMRI session leading to a difficult coordination of session dates in consideration of participants, medical doctors, free available slots and study requirements (drug exposure time). In addition, matching age groups was difficult for a number of reasons. In the first set of drugs, that was blinded by a pharmacy, the amount of placebo and levodopa tablets was not equally distributed so that in the end the number of participants that received levodopa in the first session was higher than the number of participants that received a placebo in the first session. A higher dropout rate than expected in the elderly cohort necessitated new recruitment of participants and, therefore, a new matching of participants. The high dropout was also due to several elder participants showing a low accuracy when performing the task in the scanner, although hit rate was above guessing rate in the previous training

session. In this study, the participants that were recruited had often participated in at least one functional experiment before. However, for participants being in the scanner for the first time it would have been better to familiarize participants with the unusual environment prior to testing.

In addition, because of technical and logistical reasons it was not possible to measure both age cohorts in the same scanner, meaning that several parameters were not directly comparable. Moreover, eye tracking data were assessed from the young participants to assure correct fixation at one scanner. These data were not presented in this thesis because data were not available from all participants because of technical reasons. An eye tracking system was not available in the Siemens Verio scanner meaning that the assessment of eye movement in elderly was not possible.

Despite the aforementioned difficulties in data collection, the present results are mostly in line with the current literature allowing to draw conclusions with regard to the present research questions.

7 Directions for future studies

The present thesis aimed to investigate the interaction of working memory and selective attention as well as the underlying neural correlates, and the effect of the neurotransmitters dopamine and acetylcholine. The results provide novel insights into the role of the IPC as an important node in this interaction. These findings are also novel because they were based on a paradigm which controlled for perceptual load such that attentional and memory demands could be disentangled from perceptual demands. That this interaction was only found in the anterior parts of IPC points to a functional segregation within the IPC and should be addressed in future studies. It is known that the IPC is organized in visuotopic maps (Swisher *et al.*, 2007; Silver & Kastner, 2009). An attempt to define functional segregations within IPC was made before with regard to movements (Levy *et al.*, 2007; Konen & Kastner, 2008a), representation of visual objects (Konen & Kastner, 2008b) and attention (Silver *et al.*, 2005) but an exact functional segregation in terms of memory and attention processes including distractor filtering has not been reported before. Alongside the IPC, the precuneus was found to be involved in memory processes as well. Associations with memory deficit in this thesis point to a stronger role of this brain region during memory processes than was previously assumed. Further studies addressing the exact role of the precuneus during the storage of information would provide better understanding of the neural mechanisms of memory processes. In terms of filtering, alongside the previously expected brain regions, the cerebellum moved into the fore. Filter activity in this region was reduced after levodopa administration. This relation was assumed to be based on corticocerebellar loops connecting the cerebellum with the basal ganglia

(Allen & Courchesne, 2014). Hence, the cerebellum should also be considered when investigating the dynamics of the neural correlates of selective attention.

In general, in this thesis the focus was made on the hemodynamic response during the encoding and maintenance of information. For future studies, it would be of interest to disentangle both phases to see whether successful filtering of irrelevant information, reflected in parietal activity, occurs at an early or late phase of the memory process. This could be supported by EEG measurements to understand the temporal dynamics of such processes. It was shown before that an observed filter deficit in elderly participants is based rather on a delayed filtering mechanism instead of an impairment in filtering per se (Jost *et al.*, 2011). In addition, the greater activation pattern during filtering in elderly in contrast to young participants in this thesis supports the idea of different neural mechanisms during different age phases. Likewise, in other studies similar performance in young and elderly was observed whereas the neural activity patterns differed markedly (Baltes *et al.*, 2006; Craik & Bialystok, 2006). This finding is of relevance for clinical applications. Many interventions are tested on young participants first before being used in elderly participants (Jost *et al.*, 2011). With regard to different neural mechanisms behind certain cognitive processes during aging, interventions should be more specialized on the demand of each age group.

The present data suggested that the observed impairment in hit rates during the filter conditions in the elderly was due to an impairment in frontoparietal modulated top down control. This theory is speculative based on the present data but can be tested in the future by other methods like functional connectivity analyses. In addition to reveal causal relations between brain regions involved in the addressed processes, effective connectivity methods like dynamic causal modelling or Granger causality could be used.

In the present thesis the question was addressed, whether differences in filtering and memory performance as well as hemodynamic responses in underlying neural correlates can be related to individual VWM capacity. As opposed to other studies (Todd & Marois, 2004, 2005; McNab & Klingberg, 2007; Xu & Chun, 2005) an advantage of

the present study was the measurement of individual VWM capacity from a separate task to overcome circularity effects. Contrary to expectations, VWM capacity was not related to memory related activity in IPC. Instead, associations were found with temporal areas in the elderly only. These results challenge the idea of a concrete item limit reflected in neural responses of a certain brain region and have to be kept in mind when conducting studies on individual VWM capacity differences by assuming shared limited resources as the underlying correlates of memory processes defined by task demands.

The effects of drug administration in this thesis are hard to interpret without knowing the baseline levels of the individual neurotransmitter. An attempt to control for differences was made by taking genetic and structural factors into account. However, for future studies on the effects of neurotransmitters in humans, individual differences in neurotransmitter concentration in the brain should be measured (if possible) for example by means of PET. In addition, it would be helpful to test different doses of the drug under investigation to find a dose that it most potent for the effect of interest without harming the participants. In this thesis, doses were chosen based on values reported in other studies. The present results of levodopa and galantamine administration show that their effects on memory and attention are not trivial and more studies are needed to understand the exact effect of treatment, e.g. in AD patients. Furthermore, the focus in this thesis was on drug effects on the previously defined neural correlates of filtering and memory processes. Whole brain analyses with regard to drug administration might reveal drug effects in brain regions beyond those reported here.

To confirm the genetic results found in this thesis, a larger sample would be required. In addition, several studies revealed an impact on genetic facilities on performance with regard to several genetic polymorphisms forming a pattern of a certain genotype (Greenwood *et al.*, 2009a; Stelzel *et al.*, 2009). Genetic polymorphisms that are leading to the expression of a less effective molecule (e.g. enzymes) do not necessarily imply a measurable impairment or difference between polymorphism carriers. Instead a

compensation of the impairment on a molecular level is conceivable, especially with increasing age.

Taken together the present results show an involvement of acetylcholine and dopamine in memory and attention processes which were shown to interact. Furthermore, neurodegenerative diseases like AD and PD that are characterized by dopaminergic and cholinergic deficits are better understood by examining the functional interplay of the neurotransmitters in both cognitive processes tested here. A simplified version of the paradigm reported here was tested with PD patients and patients suffering from amnestic mild cognitive impairment (aMCI, Blatt *et al.*, 2014), who have a high risk to develop AD and therefore a cholinergic deficit (Winblad *et al.*, 2004). In this study PD patients revealed a deficit in memory performance only, whereas aMCI patients showed a deficit in filtering only. Although PD patients were on dopaminergic medication when tested, deficits were still observed. Therefore, it cannot be excluded that those deficits were also due to imbalance in neurotransmitter levels with regard to acetylcholine. In addition, withdrawal of medication might have led to deficits in filtering as well. A better understanding of the effects of neurotransmitter modulation with regard to the individual baseline level is therefore of great importance for pharmacological interventions in patients suffering from neurodegenerative diseases.

8 Bibliography

Alexander, G. E., DeLong, M. R. & Strick, P. L. (**1986**). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual review of neuroscience*, 9:357–381.

Allen, G. & Courchesne, E. (**2014**). Differential effects of developmental cerebellar abnormality on cognitive and motor functions in the cerebellum: an fMRI study of autism. *American Journal of Psychiatry*, 160:262–273.

Allport, D. A. (**1977**). On knowing the meaning of words we are unable to report: The effects of visual masking. In Attention and performance VI. Lawrence Erlbaum, Hillsdale, 505–533.

Alvarez, G. A. & Cavanagh, P. (**2004**). The capacity of visual short-term memory is set both by visual information load and by number of objects. *Psychological science*, 15:106–111.

Andrews-Hanna, J. R., Snyder, A. Z., Vincent, J. L., Lustig, C., Head, D., Raichle, M. E. & Buckner, R. L. (**2007**). Disruption of large-scale brain systems in advanced aging. *Neuron*, 56:924–935.

Apud, J. A., Mattay, V., Chen, J., Kolachana, B. S., Callicott, J. H., Rasetti, R., Alce, G., Iudicello, J. E., Akbar, N., Egan, M. F. *et al.* (**2006**). Tolcapone improves cognition and cortical information processing in normal human subjects. *Neuropsychopharmacology*, 32:1011–1020.

Arabia, G., Zappia, M., Bosco, D., Crescibene, L., Bagala, A., Bastone, L., Caracciolo, M., Scornaienghi, M. & Quattrone, A. (**2002**). Body weight, levodopa pharmacokinetics and dyskinesia in Parkinson's disease. *Neurological Sciences*, 23:53–54.

Atkinson, R. C. & Shiffrin, R. M. (**1968**). Human memory: A proposed system and its control processes. *Psychology of learning and motivation*, 2:89–195.

Azam, L., Winzer-Serhan, U. & Leslie, F. (**2003**). Co-expression of $\alpha 7$ and $\beta 2$ nicotinic acetylcholine receptor subunit mRNAs within rat brain cholinergic neurons. *Neuroscience*, 119:965–977.

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S.-C. & Farde, L. (**2006**). The correlative triad among aging, dopamine, and cognition: current status and future prospects. *Neuroscience & Biobehavioral Reviews*, 30:791–807.

Baddeley, A. (**2000**). The episodic buffer: a new component of working memory? *Trends in cognitive sciences*, 4:417–423.

Baddeley, A. D. & Hitch, G. (**1974**). Working memory. *Psychology of learning and motivation*, 8:47–89.

Baddeley, A. D. & Weiskrantz, L. E. (**1993**). Working memory or working attention? In Attention: Selection, awareness, and control: A tribute to Donald Broadbent. Clarendon Press/University Press, Oxford, 152–170.

Baier, B., Kleinschmidt, A. & Müller, N. G. (**2006**). Cross-modal processing in early visual and auditory cortices depends on expected statistical relationship of multisensory information. *The Journal of neuroscience*, 26:12260–12265.

Baier, B., Müller, N. G. & Dieterich, M. (**2014**). What part of the cerebellum contributes to a visuospatial working memory task? *Annals of neurology*, 76:754–757.

Baldo, J. V. & Dronkers, N. F. (**2006**). The role of inferior parietal and inferior frontal cortex in working memory. *Neuropsychology*, 20:529–538.

Baltes, P., Lindenberger, U. & Staudinger, U. (**2006**). Life span theory in developmental psychology. In Handbook of child psychology: Vol 1, Theoretical models of human development. John Wiley & Sons Inc, 569–664.

Bartus, R. T. (**2000**). The cholinergic hypothesis a generation later. In Central nervous system diseases. Humana Press, 3–45.

Bauer, M., Kluge, C., Bach, D., Bradbury, D., Heinze, H. J., Dolan, R. J. & Driver, J. (**2012**). Cholinergic enhancement of visual attention and neural oscillations in the human brain. *Current Biology*, 22:397–402.

Bauer, R. H. & Fuster, J. M. (**1976**). Delayed-matching and delayed-response deficit from cooling dorsolateral prefrontal cortex in monkeys. *Journal of comparative and physiological psychology*, 90:293–302.

Bays, P. M. & Husain, M. (**2008**). Dynamic shifts of limited working memory resources in human vision. *Science*, 321:851–854.

Benoni, H. & Tsal, Y. (**2010**). Where have we gone wrong? Perceptual load does not affect selective attention. *Vision research*, 50:1292–1298.

Benoni, H. & Tsal, Y. (**2012**). Controlling for dilution while manipulating load: perceptual and sensory limitations are just two aspects of task difficulty. *Psychonomic bulletin & review*, 19:631–638.

Bentley, P., Driver, J. & Dolan, R. (**2009**). Modulation of fusiform cortex activity by cholinesterase inhibition predicts effects on subsequent memory. *Brain*, 132:2356–2371.

Bentley, P., Vuilleumier, P., Thiel, C. M., Driver, J. & Dolan, R. J. (**2003**). Cholinergic enhancement modulates neural correlates of selective attention and emotional processing. *Neuroimage*, 20:58–70.

Bierer, L. M., Haroutunian, V., Gabriel, S., Knott, P. J., Carlin, L. S., Purohit, D. P., Perl, D. P., Schmeidler, J., Kanof, P. & Davis, K. L. (**1995**). Neurochemical correlates of dementia severity in Alzheimer's disease: relative importance of the cholinergic deficits. *Journal of neurochemistry*, 64:749–760.

Blaschko, H. (**1952**). Amine oxidase and amine metabolism. *Pharmacological reviews*, 4:415–458.

Blatt, J., Vellage, A., Baier, B. & Müller, N. G. (**2014**). The contribution of acetylcholine and dopamine to subprocesses of visual working memory - What patients with amnestic mild cognitive impairment and Parkinson's disease can tell us. *Neuropsychologia*, 61:89–95.

Bočková, M., Chládek, J., Jurák, P., Halámek, J., Baláž, M. & Rektor, I. (**2011**). Involvement of the subthalamic nucleus and globus pallidus internus in attention. *Journal of neural transmission*, 118:1235–1245.

Brady, T. F., Konkle, T. & Alvarez, G. A. (**2011**). A review of visual memory capacity: Beyond individual items and toward structured representations. *Journal of vision*, 11:1–34.

Brefczynski, J. A. & DeYoe, E. A. (**1999**). A physiological correlate of the'spotlight'of visual attention. *Nature neuroscience*, 2:370–374.

Brett, M., Anton, J., Valabregue, R. & Poline, J. (**2002**). Region of interest analysis using an SPM toolbox [abstract/497] presented at the 8th International Conference on Functional Mapping of the Human Brain, June 2–6, Sendai, Japan. *NeuroImage*, 16.

Brickenkamp, R. (**1962**). Test d2: Aufmerksamkeits-Belastungs-Test. Hogrefe Verlag für Psychologie, Göttingen.

Broadbent, D. E. (**1957**). A mechanical model for human attention and immediate memory. *Psychological Review*, 64:205–215.

Broadbent Donald, E. (**1958**). Perception and communication. Pergamon Press, Oxford.

Brozoski, T. J., Brown, R. M., Rosvold, H. & Goldman, P. S. (**1979**). Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. *Science*, 205:929–932.

Bruce, C. J. & Goldberg, M. E. (**1985**). Primate frontal eye fields. I. Single neurons discharging before saccades. *Journal of Neurophysiology*, 53:603–635.

Bruce, C. J., Goldberg, M. E., Bushnell, M. C. & Stanton, G. B. (**1985**). Primate frontal eye fields. II. Physiological and anatomical correlates of electrically evoked eye movements. *Journal of neurophysiology*, 54:714–734.

Burgess, P. W., Dumontheil, I. & Gilbert, S. J. (**2007**a). The gateway hypothesis of rostral prefrontal cortex (area 10) function. *Trends in cognitive sciences*, 11:290–298.

Burgess, P. W., Gilbert, S. J. & Dumontheil, I. (**2007**b). Function and localization within rostral prefrontal cortex (area 10). *Philosophical Transactions of the Royal Society B: Biological Sciences*, 362:887–899.

Cabeza, R., Anderson, N. D., Locantore, J. K. & McIntosh, A. R. (**2002**). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage*, 17:1394–1402.

Cabeza, R., Daselaar, S. M., Dolcos, F., Prince, S. E., Budde, M. & Nyberg, L. (**2004**). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cerebral cortex*, 14:364–375.

Calabresi, P., Picconi, B., Parnetti, L. & Di Filippo, M. (**2006**). A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine–acetylcholine synaptic balance. *The Lancet Neurology*, 5:974–983.

Cavanagh, P. & Alvarez, G. A. (**2005**). Tracking multiple targets with multifocal attention. *Trends in cognitive sciences*, 9:349–354.

Cave, K. R. & Bichot, N. P. (**1999**). Visuospatial attention: Beyond a spotlight model. *Psychonomic Bulletin & Review*, 6:204–223.

Chafee, M. V. & Goldman-Rakic, P. S. (**1998**). Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. *Journal of Neurophysiology*, 79:2919–2940.

Chao, L. L. & Knight, R. T. (**1995**). Human prefrontal lesions increase distractibility to irrelevant sensory inputs. *Neuroreport*, 6:1605–1610.

Chen, J., Lipska, B. K., Halim, N., Ma, Q. D., Matsumoto, M., Melhem, S., Kolachana, B. S., Hyde, T. M., Herman, M. M., Apud, J. *et al.* (**2004**). Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): Effects on mRNA, protein, and enzyme activity in postmortem human brain. *The American Journal of Human Genetics*, 75:807–821.

Cherry, E. C. (**1953**). Some experiments on the recognition of speech, with one and with two ears. *The Journal of the acoustical society of America*, 25:975–979.

Civelli, O., Bunzow, J. R. & Grandy, D. K. (**1993**). Molecular diversity of the dopamine receptors. *Annual review of pharmacology and toxicology*, 33:281–307.

Clark, K. L. & Noudoost, B. (**2014**). The role of prefrontal catecholamines in attention and working memory. *Frontiers in neural circuits*, 8:1–19.

Clarke, C. E. (**2004**). Neuroprotection and pharmacotherapy for motor symptoms in Parkinson's disease. *The Lancet Neurology*, 3:466–474.

Čolović, M. B., Krstić, D. Z., Lazarević-Pašti, T. D., Bondžić, A. M. & Vasić, V. M. (**2013**). Acetylcholinesterase inhibitors: Pharmacology and toxicology. *Current neuropharmacology*, 11:315–335.

Cools, R., Barker, R. A., Sahakian, B. J. & Robbins, T. W. (**2001**). Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cerebral Cortex*, 11:1136–1143.

Cools, R. & D'Esposito, M. (**2011**). Inverted-U-shaped Dopamine actions on human working memory and cognitive control. *Biological psychiatry*, 69:113–125.

Cools, R., Gibbs, S. E., Miyakawa, A., Jagust, W. & D'Esposito, M. (**2008**). Working memory capacity predicts dopamine synthesis capacity in the human striatum. *The Journal of Neuroscience*, 28:1208–1212.

Cools, R., Miyakawa, A., Sheridan, M. & D'Esposito, M. (**2009**). Enhanced frontal function in Parkinson's disease. *Brain*, 133:225–233.

Cools, R., Sheridan, M., Jacobs, E. & D'Esposito, M. (**2007**). Impulsive personality predicts dopamine-dependent changes in frontostriatal activity during component processes of working memory. *The Journal of neuroscience*, 27:5506–5514.

Corbetta, M., Akbudak, E., Conturo, T. E., Snyder, A. Z., Ollinger, J. M., Drury, H. A., Linenweber, M. R., Petersen, S. E., Raichle, M. E., Van Essen, D. C. *et al.* (**1998**). A common network of functional areas for attention and eye movements. *Neuron*, 21:761–773.

Corbetta, M., Kincade, M. J., Lewis, C., Snyder, A. Z. & Sapir, A. (**2005**). Neural basis and recovery of spatial attention deficits in spatial neglect. *Nature neuroscience*, 8:1603–1610.

Corbetta, M., Patel, G. & Shulman, G. L. (**2008**). The reorienting system of the human brain: from environment to theory of mind. *Neuron*, 58:306–324.

Corbetta, M. & Shulman, G. L. (**2002**). Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews neuroscience*, 3:201–215.

Cowan, N. (**1988**). Evolving conceptions of memory storage, selective attention, and their mutual constraints within the human information-processing system. *Psychological bulletin*, 104:163.

Cowan, N. (**1995**). Attention and memory: An integrated framework. Oxford Psychology Series, New York.

Cowan, N. (**2001**). The magical number 4 in short-term memory: a reconsideration of mental storage capacity. *Behavioral Brain Sciences*, 24:87–114.

Cowan, N. (**2004**). Working memory capacity. Psychology Press, New York.

Cowan, N. (**2010**). The magical mystery four - How is working memory capacity limited, and why? *Current Directions in Psychological Science*, 19:51–57.

Craik, F. I. & Bialystok, E. (**2006**). Cognition through the lifespan: mechanisms of change. *Trends in cognitive sciences*, 10:131–138.

Crum, R. M., Anthony, J. C., Bassett, S. S. & Folstein, M. F. (**1993**). Population-based norms for the Mini-Mental State Examination by age and educational level. *Journal of the American Medical Association*, 269:2386–2391.

Cubells, J., Kranzler, H., McCance-Katz, E., Anderson, G., Malison, R., Price, L. & Gelernter, J. (**2000**). A haplotype at the DBH locus, associated with low plasma dopamine beta-hydroxylase activity, also associates with cocaine-induced paranoia. *Molecular psychiatry*, 5:56–63.

Cubells, J. F., van Kammen, D. P., Kelley, M. E., Anderson, G. M., O'Connor, D. T., Price, L. H., Malison, R., Rao, P. A., Kobayashi, K., Nagatsu, T. *et al.* (**1998**). Dopamine β-hydroxylase: two polymorphisms in linkage disequilibrium at the structural gene DBH associate with biochemical phenotypic variation. *Human genetics*, 102:533–540.

Culham, J. C., Cavanagh, P. & Kanwisher, N. G. (**2001**). Attention response functions: characterizing brain areas using fMRI activation during parametric variations of attentional load. *Neuron*, 32:737–745.

Dale, H. (**1937**). Transmission of nervous effects by acetylcholine: Harvey Lecture, May 20, 1937. *Bulletin of the New York Academy of Medicine*, 13:379.

Dale, H. H. (**1914**). The action of certain esters and ethers of choline and their relation to muscarine. *Journal of Pharmacology and Experimental Therapeutics*, 6:147–190.

Damoiseaux, J., Beckmann, C., Arigita, E. S., Barkhof, F., Scheltens, P., Stam, C., Smith, S. & Rombouts, S. (**2008**). Reduced resting-state brain activity in the "default network" in normal aging. *Cerebral cortex*, 18:1856–1864.

Daneman, M. & Carpenter, P. A. (**1980**). Individual differences in working memory and reading. *Journal of verbal learning and verbal behavior*, 19:450–466.

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S. & Cabeza, R. (**2008**). Que PASA? The posterior–anterior shift in aging. *Cerebral cortex*, 18:1201–1209.

De Fockert, J. W. (**2013**). Beyond perceptual load and dilution: a review of the role of working memory in selective attention. *Frontiers in psychology*, 4:284–296.

De Fockert, J. W., Rees, G., Frith, C. D. & Lavie, N. (**2001**). The role of working memory in visual selective attention. *Science*, 291:1803–1806.

Desimone, R. & Duncan, J. (**1995**). Neural mechanisms of selective visual attention. *Annual review of neuroscience*, 18:193–222.

Deutsch, J. A. & Deutsch, D. (**1963**). Attention: some theoretical considerations. *Psychological review*, 70:80–90.

Dewey, S., Volkow, N., Logan, J., MacGregor, R., Fowler, J., Schlyer, D. & Bendriem, B. (**1990**). Age-related decreases in muscarinic cholinergic receptor binding in the human brain measured with positron emission tomography (PET). *Journal of neuroscience research*, 27:569–575.

Doricchi, F., de Schotten, M. T., Tomaiuolo, F. & Bartolomeo, P. (**2008**). White matter (dis) connections and gray matter (dys) functions in visual neglect: gaining insights into the brain networks of spatial awareness. *Cortex*, 44:983–995.

Downing, P. E. (**2000**). Interactions between visual working memory and selective attention. *Psychological Science*, 11:467–473.

Dubois, B. & Pillon, B. (**1996**). Cognitive deficits in Parkinson's disease. *Journal of neurology*, 244:2–8.

Duncan, J. (**1980**). The locus of interference in the perception of simultaneous stimuli. *Psychological review*, 87:272–300.

Dunlop, B. W. & Nemeroff, C. B. (**2007**). The role of dopamine in the pathophysiology of depression. *Archives of General Psychiatry*, 64:327–337.

Durstewitz, D., Seamans, J. K. & Sejnowski, T. J. (**2000**). Neurocomputational models of working memory. *Nature neuroscience*, 3:1184–1191.

Düzel, S., Schütze, H., Stallforth, S., Kaufmann, J., Bodammer, N., Bunzeck, N., Münte, T. F., Lindenberger, U., Heinze, H.-J. & Düzel, E. (**2008**). A close relationship between verbal memory and SN/VTA integrity in young and older adults. *Neuropsychologia*, 46:3042–3052.

Eckert, T., Sailer, M., Kaufmann, J., Schrader, C., Peschel, T., Bodammer, N., Heinze, H.-J. & Schoenfeld, M. A. (**2004**). Differentiation of idiopathic Parkinson's disease, multiple system atrophy, progressive supranuclear palsy, and healthy controls using magnetization transfer imaging. *Neuroimage*, 21:229–235.

Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., Goldman, D. & Weinberger, D. R. (**2001**). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences*, 98:6917–6922.

Eisenberg, J., Mei-Tal, G., Steinberg, A., Tartakovsky, E., Zohar, A., Gritsenko, I., Nemanov, L. & Ebstein, R. P. (**1999**). Haplotype relative risk study of catechol-O-methyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD): Association of the high-enzyme activity val allele with ADHD impulsive-hyperactive phenotype. *American journal of medical genetics*, 88:497–502.

Emre, M., Aarsland, D., Albanese, A., Byrne, E. J., Deuschl, G., De Deyn, P. P., Durif, F., Kulisevsky, J., van Laar, T., Lees, A. *et al.* (**2004**). Rivastigmine for dementia associated with Parkinson's disease. *New England Journal of Medicine*, 351:2509–2518.

Engle, R. W., Kane, M. J., Tuholski, S. W. *et al.* (**1999**). Individual differences in working memory capacity and what they tell us about controlled attention, general fluid intelligence, and functions of the prefrontal cortex. In Models of working memory: Mechanisms of active maintenance and executive control. University Press, Cambridge, 102–134.

Eriksen, C. W. & James, J. D. S. (**1986**). Visual attention within and around the field of focal attention: A zoom lens model. *Perception & psychophysics*, 40:225–240.

Erixon-Lindroth, N., Farde, L., Robins Wahlin, T.-B., Sovago, J., Halldin, C. & Bäckman, L. (**2005**). The role of the striatal dopamine transporter in cognitive aging. *Psychiatry Research: Neuroimaging*, 138:1–12.

Espeseth, T., Sneve, M. H., Rootwelt, H. & Laeng, B. (**2010**). Nicotinic receptor gene CHRNA4 interacts with processing load in attention. *Public Library of Science One*, 5:e14407.

Fecteau, J. H., Bell, A. H. & Munoz, D. P. (**2004**). Neural correlates of the automatic and goal-driven biases in orienting spatial attention. *Journal of Neurophysiology*, 92:1728–1737.

Feredoes, E., Heinen, K., Weiskopf, N., Ruff, C. & Driver, J. (**2011**). Causal evidence for frontal involvement in memory target maintenance by posterior brain areas during distracter interference of visual working memory. *Proceedings of the National Academy of Sciences*, 108:17510–17515.

Finke, K., Bublak, P. & Zihl, J. (**2006**). Visual spatial and visual pattern working memory: Neuropsychological evidence for a differential role of left and right dorsal visual brain. *Neuropsychologia*, 44:649–661.

Folstein, M. F., Folstein, S. E. & McHugh, P. R. (**1975**). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research*, 12:189–198.

Fougnie, D. & Marois, R. (**2006**). Distinct Capacity Limits for Attention and Working Memory Evidence From Attentive Tracking and Visual Working Memory Paradigms. *Psychological Science*, 17:526–534.

Frank, M. J., Loughry, B. & O'Reilly, R. C. (**2001**). Interactions between frontal cortex and basal ganglia in working memory: a computational model. *Cognitive, Affective, & Behavioral Neuroscience*, 1:137–160.

Friedman-Hill, S. R., Robertson, L. C., Desimone, R. & Ungerleider, L. G. (**2003**). Posterior parietal cortex and the filtering of distractors. *Proceedings of the National Academy of Sciences*, 100:4263–4268.

Friedman-Hill SR, T. A., Robertson LC (**1995**). Parietal contributions to visual feature binding: evidence from a patient with bilateral lesions. *Science*, 269:853–855.

Friston, K., Ashburner, J., Frith, C. D., Poline, J.-B., Heather, J. D., Frackowiak, R. S. *et al.* (**1995**). Spatial registration and normalization of images. *Human brain mapping*, 3:165–189.

Fukuda, K., Vogel, E., Mayr, U. & Awh, E. (**2010**). Quantity, not quality: The relationship between fluid intelligence and working memory capacity. *Psychonomic bulletin & review*, 17:673–679.

Funahashi, S., Bruce, C. J. & Goldman-Rakic, P. S. (**1993**). Dorsolateral prefrontal lesions and oculomotor delayed-response performance: evidence for mnemonic "scotomas". *The Journal of Neuroscience*, 13:1479–1497.

Furey, M. L., Pietrini, P. & Haxby, J. V. (**2000**). Cholinergic enhancement and increased selectivity of perceptual processing during working memory. *Science*, 290:2315–2319.

Furey, M. L., Pietrini, P., Haxby, J. V. & Drevets, W. C. (**2007**). Selective effects of cholinergic modulation on task performance during selective attention. *Neuropsychopharmacology*, 33:913–923.

Fuster, J. M. (**1973**). Unit activity in prefrontal cortex during delayed-response performance: neuronal correlates of transient memory. *Journal of Neurophysiology*, 36:61–78.

Fuster, J. M. & Alexander, G. E. (**1971**). Neuron activity related to short-term memory. *Science*, 173:652–654.

Gandhi, S. P., Heeger, D. J. & Boynton, G. M. (**1999**). Spatial attention affects brain activity in human primary visual cortex. *Proceedings of the National Academy of Sciences*, 96:3314–3319.

Garris, P. A., Collins, L. B., Jones, S. R. & Wightman, R. M. (**1993**). Evoked extracellular dopamine in vivo in the medial prefrontal cortex. *Journal of neurochemistry*, 61:637–647.

Gaspar, P., Berger, B., Febvret, A., Vigny, A. & Henry, J. P. (**1989**). Catecholamine innervation of the human cerebral cortex as revealed by comparative immunohistochemistry of tyrosine hydroxylase and dopamine-beta-hydroxylase. *Journal of Comparative Neurology*, 279:249–271.

Gazzaley, A., Clapp, W., Kelley, J., McEvoy, K., Knight, R. T. & D'Esposito, M. (**2008**). Age-related top-down suppression deficit in the early stages of cortical visual memory processing. *Proceedings of the National Academy of Sciences*, 105:13122–13126.

Gazzaley, A., Cooney, J. W., D'Esposito, M. & Rissman, J. (**2005**a). Top-down suppression deficit underlies working memory impairment in normal aging. *Nature neuroscience*, 8:1298–1300.

Gazzaley, A., Cooney, J. W., McEvoy, K., Knight, R. T. & D'esposito, M. (**2005**b). Top-down enhancement and suppression of the magnitude and speed of neural activity. *Journal of cognitive neuroscience*, 17:507–517.

Geerligs, L., Saliasi, E., Maurits, N. M., Renken, R. J. & Lorist, M. M. (**2014**). Brain mechanisms underlying the effects of aging on different aspects of selective attention. *NeuroImage*, 91:52–62.

Gibbs, S. E. & D'Esposito, M. (**2005**). Individual capacity differences predict working memory performance and prefrontal activity following dopamine receptor stimulation. *Cognitive, Affective, & Behavioral Neuroscience*, 5:212–221.

Goldman-Rakic, P. S. (**1987**). Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In Handbook of Physiology: The Nervous System. Wiley Online Library, 373–417.

Gorelova, N. A. & Yang, C. R. (**2000**). Dopamine D1/D5 receptor activation modulates a persistent sodium current in rat prefrontal cortical neurons in vitro. *Journal of Neurophysiology*, 84:75–87.

Gotti, C., Zoli, M. & Clementi, F. (**2006**). Brain nicotinic acetylcholine receptors: native subtypes and their relevance. *Trends in pharmacological sciences*, 27:482–491.

Gousias, I. S., Rueckert, D., Heckemann, R. A., Dyet, L. E., Boardman, J. P., Edwards, A. D. & Hammers, A. (**2008**). Automatic segmentation of brain MRIs of 2-year-olds into 83 regions of interest. *Neuroimage*, 40:672–684.

Graubner, B. (**2013**). ICD-10-GM 2014 Systematisches Verzeichnis: Internationale statistische Klassifikation der Krankheiten und verwandter Gesundheitsprobleme, 11. Revision - German Modification, Version 2014. Deutscher Ärzteverlag.

Greenwood, P., Lin, M.-K., Sundararajan, R., Fryxell, K. & Parasuraman, R. (**2009**a). Synergistic effects of genetic variation in nicotinic and muscarinic receptors on visual attention but not working memory. *Proceedings of the National Academy of Sciences*, 106:3633–3638.

Greenwood, P., Parasuraman, R. & Espeseth, T. (**2012**). A cognitive phenotype for a polymorphism in the nicotinic receptor gene CHRNA4. *Neuroscience & Biobehavioral Reviews*, 36:1331–1341.

Greenwood, P. M., Sundararajan, R., Lin, M.-K., Kumar, R., Fryxell, K. J. & Parasuraman, R. (**2009**b). Both a nicotinic single nucleotide polymorphism (SNP) and a noradrenergic SNP modulate working memory performance when attention is manipulated. *Journal of cognitive neuroscience*, 21:2139–2153.

Grill-Spector, K., Kushnir, T., Hendler, T. & Malach, R. (**2000**). The dynamics of object-selective activation correlate with recognition performance in humans. *Nature neuroscience*, 3:837–843.

Grinberg, L. T., de Lucena Ferretti, R. E., Farfel, J. M., Leite, R., Pasqualucci, C. A., Rosemberg, S., Nitrini, R., Saldiva, P. H. N., Jacob Filho, W., Group, B. A. B. S. *et al.* (**2007**). Brain bank of the Brazilian aging brain study group — a milestone reached and more than 1,600 collected brains. *Cell and tissue banking*, 8:151–162.

Gruber, A. J., Dayan, P., Gutkin, B. S. & Solla, S. A. (**2006**). Dopamine modulation in the basal ganglia locks the gate to working memory. *Journal of computational neuroscience*, 20:153–166.

Guillery, R. & Sherman, S. M. (**2002**). Thalamic relay functions and their role in corticocortical communication: generalizations from the visual system. *Neuron*, 33:163–175.

Gutchess, A., Welsh, R., Hedden, T., Bangert, A., Minear, M., Liu, L. & Park, D. (**2005**). Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. *Journal of Cognitive Neuroscience*, 17:84–96.

Haber, S. & Mcfarland, N. R. (**2001**). The place of the thalamus in frontal cortical-basal ganglia circuits. *The Neuroscientist*, 7:315–324.

Haggard, P. & Whitford, B. (**2004**). Supplementary motor area provides an efferent signal for sensory suppression. *Cognitive Brain Research*, 19:52–58.

Hammers, A., Allom, R., Koepp, M. J., Free, S. L., Myers, R., Lemieux, L., Mitchell, T. N., Brooks, D. J. & Duncan, J. S. (**2003**). Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. *Human brain mapping*, 19:224–247.

Handy, T. C., Borg, J. S., Turk, D. J., Tipper, C. M., Grafton, S. T. & Gazzaniga, M. S. (**2005**). Placing a tool in the spotlight: spatial attention modulates visuomotor responses in cortex. *NeuroImage*, 26:266–276.

Hasher, L. & Zacks, R. T. (**1988**). Working memory, comprehension, and aging: A review and a new view. *Psychology of learning and motivation*, 22:193–225.

Hazy, T. E., Frank, M. J. & O'Reilly, R. C. (**2007**). Towards an executive without a homunculus: computational models of the prefrontal cortex/basal ganglia

system. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 362:1601–1613.

Heinemann, L., Kleinschmidt, A. & Müller, N. G. (**2009**). Exploring BOLD changes during spatial attention in non-stimulated visual cortex. *Public Library of Science One*, 4:e5560.

Heinze, H., Mangun, G., Burchert, W., Hinrichs, H., Scholz, M., Münte, T., Gös, A., Scherg, M., Johannes, S., Hundeshagen *et al.* (**1994**). Combined spatial and temporal imaging of brain activity during visual selective attention in humans. *Nature*, 372:543–546.

Herrero, J., Roberts, M., Delicato, L., Gieselmann, M., Dayan, P. & Thiele, A. (**2008**). Acetylcholine contributes through muscarinic receptors to attentional modulation in V1. *Nature*, 454:1110–1114.

Heun, R., Freymann, K., Erb, M., Leube, D. T., Jessen, F., Kircher, T. T. & Grodd, W. (**2005**). Successful verbal retrieval in elderly subjects is related to concurrent hippocampal and posterior cingulate activation. *Dementia and geriatric cognitive disorders*, 22:165–172.

Hillyard, S. A. & Mangun, G. R. (**1987**). Sensory gating as a physiological mechanism for visual selective attention. *Electroencephalography and Clinical Neurophysiology*, 40:61–67.

Hopf, J.-M., Boehler, C., Luck, S., Tsotsos, J., Heinze, H.-J. & Schoenfeld, M. (**2006**). Direct neurophysiological evidence for spatial suppression surrounding the focus of attention in vision. *Proceedings of the National Academy of Sciences of the United States of America*, 103:1053–1058.

Hopfinger, J. B., Jha, A. P., Hopf, J.-M., Girelli, M. & Mangun, G. R. (**2000**a). Electrophysiological and neuroimaging studies of voluntary and reflexive attention. In Attention and performance XVII. MIT Press, Cambridge, 125–153.

Hopfinger, J. B., Mangun, G. R. & Buonocore, M. H. (**2000**b). The neural mechanisms of top-down attentional control. *Nature neuroscience*, 3:284–291.

Irwin, D. & Gordon, R. (**1998**). Eye movements, attention and trans-saccadic memory. *Visual Cognition*, 5:127–155.

Jech, R., Mueller, K., Schroeter, M. L. & Ruzicka, E. (**2013**). Levodopa increases functional connectivity in the cerebellum and brainstem in Parkinson's disease. *Brain*, 136:e234–e234.

Jellinger, K. (**2000**). Morphological substrates of mental dysfunction in Lewy body disease: an update. *Journal of Neural Transmission*, 59:185–212.

Jeneson, A. & Squire, L. R. (**2012**). Working memory, long-term memory, and medial temporal lobe function. *Learning & Memory*, 19:15–25.

Jost, K., Bryck, R. L., Vogel, E. K. & Mayr, U. (**2011**). Are old adults just like low working memory young adults? Filtering efficiency and age differences in visual working memory. *Cerebral Cortex*, 21:1147–1154.

Kaasinen, V. & Rinne, J. O. (**2002**). Functional imaging studies of dopamine system and cognition in normal aging and Parkinson's disease. *Neuroscience & Biobehavioral Reviews*, 26:785–793.

Kaasinen, V., Vilkman, H., Hietala, J., Någren, K., Helenius, H., Olsson, H., Farde, L. & Rinne, J. O. (**2000**). Age-related dopamine D2/D3 receptor loss in extrastriatal regions of the human brain. *Neurobiology of aging*, 21:683–688.

Kane, M. J., Bleckley, M. K., Conway, A. R. & Engle, R. W. (**2001**). A controlled-attention view of working-memory capacity. *Journal of Experimental Psychology: General*, 130:169–183.

Kanwisher, N., McDermott, J. & Chun, M. M. (**1997**). The fusiform face area: a module in human extrastriate cortex specialized for face perception. *The Journal of Neuroscience*, 17:4302–4311.

Kastner, S. & Ungerleider, L. G. (**2001**). The neural basis of biased competition in human visual cortex. *Neuropsychologia*, 39:1263–1276.

Kavanagh, S., Howe, I., Brashear, H., Wang, D., Van Baelen, B., Todd, M. & Schwalen, S. (**2011**). Long-term response to galantamine in relation to short-term efficacy data: pooled analysis in patients with mild to moderate Alzheimer's disease. *Current Alzheimer Research*, 8:175–186.

Kilimann, I., Grothe, M., Heinsen, H., Alho, E. J. L., Grinberg, L., Amaro Jr, E., Dos Santos, G. A. B., da Silva, R. E., Mitchell, A. J., Frisoni, G. B. *et al.* (**2014**). Subregional basal forebrain atrophy in Alzheimer's disease: a multicenter study. *Journal of Alzheimer's Disease*, 40:687–700.

Kimberg, D. Y. & D'Esposito, M. (**2003**). Cognitive effects of the dopamine receptor agonist pergolide. *Neuropsychologia*, 41:1020–1027.

Kimberg, D. Y., D'Esposito, M. & Farah, M. J. (**1997**). Effects of bromocriptine on human subjects depend on working memory capacity. *Neuroreport*, 8:3581–3585.

Kincade, J. M., Abrams, R. A., Astafiev, S. V., Shulman, G. L. & Corbetta, M. (**2005**). An event-related functional magnetic resonance imaging study of voluntary and stimulus-driven orienting of attention. *The Journal of Neuroscience*, 25:4593–4604.

Kirchner, W. K. (**1958**). Age differences in short-term retention of rapidly changing information. *Journal of experimental psychology*, 55:352–358.

Kiyonaga, A. & Egner, T. (**2013**). Working memory as internal attention: Toward an integrative account of internal and external selection processes. *Psychonomic bulletin & review*, 20:228–242.

Klinkenberg, I., Sambeth, A. & Blokland, A. (**2011**). Acetylcholine and attention. *Behavioural brain research*, 221:430–442.

Knecht, S., Breitenstein, C., Bushuven, S., Wailke, S., Kamping, S., Flöel, A., Zwitserlood, P. & Ringelstein, E. B. (**2004**). Levodopa: faster and better word learning in normal humans. *Annals of neurology*, 56:20–26.

Komatsu, H. & Suzuki, H. (**1985**). Projections from the functional subdivisions of the frontal eye field to the superior colliculus in the monkey. *Brain research*, 327:324–327.

Konen, C. S. & Kastner, S. (**2008**a). Representation of eye movements and stimulus motion in topographically organized areas of human posterior parietal cortex. *The Journal of Neuroscience*, 28:8361–8375.

Konen, C. S. & Kastner, S. (**2008**b). Two hierarchically organized neural systems for object information in human visual cortex. *Nature neuroscience*, 11:224–231.

Kori, A., Miyashita, N., Kato, M., Hikosaka, O., Usui, S. & Matsumura, M. (**1995**). Eye movements in monkeys with local dopamine depletion in the caudate nucleus. II. Deficits in voluntary saccades. *The Journal of neuroscience*, 15:928–941.

Kozlovskiy, S. A., Vartanov, A. V., Nikonova, E. Y., Pyasik, M. M. & Velichkovsky, B. M. (**2012**). The cingulate cortex and human memory processes. *Psychology in Russia: State of the art*, 5:231–243.

LaBar, K. S., Gitelman, D. R., Parrish, T. B. & Mesulam, M.-M. (**1999**). Neuroanatomic overlap of working memory and spatial attention networks: a functional MRI comparison within subjects. *Neuroimage*, 10:695–704.

LaBerge, D. (**1975**). Acquisition of automatic processing in perceptual and associative learning. In Attention and performance V. Academic Press, New York, 50–64.

LaBerge, D. (**2002**). Attentional control: brief and prolonged. *Psychological research*, 66:220–233.

Landau, S. M., Lal, R., O'Neil, J. P., Baker, S. & Jagust, W. J. (**2009**). Striatal dopamine and working memory. *Cerebral Cortex*, 19:445–454.

Lavie, N. (**1995**). Perceptual load as a necessary condition for selective attention. *Journal of Experimental Psychology: Human Perception and Performance*, 21:451–468.

Lavie, N. & De Fockert, J. (**2005**). The role of working memory in attentional capture. *Psychonomic Bulletin & Review*, 12:669–674.

Lavie, N. & Tsal, Y. (**1994**). Perceptual load as a major determinant of the locus of selection in visual attention. *Perception & Psychophysics*, 56:183–197.

Le, T. H., Pardo, J. V. & Hu, X. (**1998**). 4 T-fMRI study of nonspatial shifting of selective attention: cerebellar and parietal contributions. *Journal of Neurophysiology*, 79:1535–1548.

Léna, C. & Changeux, J.-P. (**1998**). Allosteric nicotinic receptors, human pathologies. *Journal of Physiology-Paris*, 92:63–74.

Lepsien, J. & Nobre, A. C. (**2006**). Cognitive control of attention in the human brain: Insights from orienting attention to mental representations. *Brain research*, 1105:20–31.

Levin, B. E., Tomer, R. & Rey, G. J. (**1992**). Cognitive impairments in Parkinson's disease. *Neurologic clinics*, 10:471–485.

Levy, I., Schluppeck, D., Heeger, D. J. & Glimcher, P. W. (**2007**). Specificity of human cortical areas for reaches and saccades. *The Journal of neuroscience*, 27:4687–4696.

Li, S.-C., Lindenberger, U. & Bäckman, L. (**2010**). Dopaminergic modulation of cognition across the life span. *Neuroscience & Biobehavioral Reviews*, 34:625–630.

Li, S.-C. & Rieckmann, A. (**2014**). Neuromodulation and aging: implications of aging neuronal gain control on cognition. *Current opinion in neurobiology*, 29:148–158.

Lindenberger, U., Burzynska, A. & I.E., N. (**2013**). Heterogeneity in frontal-lobe aging. In Principles of frontal lobe function. University Press, Oxford, 609–627.

Lledo, A., Hundermer, H., Van Laar, T., Quail, D., Rost, N., Nohria, V., Wolters, E., Schwarz, J. & Oertel, W. (**2000**). Long-term efficacy of pergolide monotherapy in early-stage Parkinson's disease. One-year interim analysis of a 3-year double-blind, randomized study versus levodopa. *Movement Disorders*, 15:115–126.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T. & Oeltermann, A. (**2001**). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, 412:150–157.

Luciana, M. & Collins, P. F. (**1997**). Dopaminergic modulation of working memory for spatial but not object cues in normal humans. *Journal of cognitive neuroscience*, 9:330–347.

Luck, S. J. & Vogel, E. K. (**1997**). The capacity of visual working memory for features and conjunctions. *Nature*, 390:279–281.

Maddock, R., Garrett, A. & Buonocore, M. (**2001**). Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. *Neuroscience*, 104:667–676.

Magen, H., Emmanouil, T.-A., McMains, S. A., Kastner, S. & Treisman, A. (**2009**). Attentional demands predict short-term memory load response in posterior parietal cortex. *Neuropsychologia*, 47:1790–1798.

Markett, S. A., Montag, C. & Reuter, M. (**2010**). The association between dopamine DRD2 polymorphisms and working memory capacity is modulated by a functional polymorphism on the nicotinic receptor gene CHRNA4. *Journal of cognitive neuroscience*, 22:1944–1954.

Martinez, A., Anllo-Vento, L., Sereno, M. I., Frank, L. R., Buxton, R. B., Dubowitz, D., Wong, E. C., Hinrichs, H., Heinze, H. J. & Hillyard, S. A. (**1999**). Involvement of striate and extrastriate visual cortical areas in spatial attention. *Nature neuroscience*, 2:364–369.

Mathôt, S., Hickey, C. & Theeuwes, J. (**2010**). From reorienting of attention to biased competition: Evidence from hemifield effects. *Attention, Perception, & Psychophysics*, 72:651–657.

Matsuyoshi, D., Ikeda, T., Sawamoto, N., Kakigi, R., Fukuyama, H., Osaka, N. & Greenlee, M. W. (**2012**). Differential Roles for Parietal and Occipital Cortices in Visual Working Memory. *Public Library of Science ONE*, 7:e38623.

Matsuyoshi, D., Osaka, M. & Osaka, N. (**2014**). Age and individual differences in visual working memory deficit induced by overload. *Frontiers in psychology*, 5:1–7.

Mattay, V. S., Callicott, J. H., Bertolino, A., Heaton, I., Frank, J. A., Coppola, R., Berman, K. F., Goldberg, T. E. & Weinberger, D. R. (**2000**). Effects of dextroamphetamine on cognitive performance and cortical activation. *Neuroimage*, 12:268–275.

Mattay, V. S., Goldberg, T. E., Fera, F., Hariri, A. R., Tessitore, A., Egan, M. F., Kolachana, B., Callicott, J. H. & Weinberger, D. R. (**2003**). Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proceedings of the National Academy of Sciences*, 100:6186–6191.

Mayer, J. S., Bittner, R. A., Nikolić, D., Bledowski, C., Goebel, R. & Linden, D. E. (**2007**). Common neural substrates for visual working memory and attention. *Neuroimage*, 36:441–453.

McHaffie, J. G., Stanford, T. R., Stein, B. E., Coizet, V. & Redgrave, P. (**2005**). Subcortical loops through the basal ganglia. *Trends in neurosciences*, 28:401–407.

McNab, F. & Klingberg, T. (**2007**). Prefrontal cortex and basal ganglia control access to working memory. *Nature neuroscience*, 11:103–107.

Mehta, M. A., Owen, A. M., Sahakian, B. J., Mavaddat, N., Pickard, J. D. & Robbins, T. W. (**2000**). Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. *J Neurosci*, 20:651–656.

Mentis, M. J., Sunderland, T., Lai, J., Connolly, C., Krasuski, J., Levine, B., Friz, J., Sobti, S., Schapiro, M. & Rapoport, S. I. (**2001**). Muscarinic versus nicotinic modulation of a visual task: a PET study using drug probes. *Neuropsychopharmacology*, 25:555–564.

Mesulam, M. (**2004**). The cholinergic lesion of Alzheimer's disease: pivotal factor or side show? *Learning & Memory*, 11:43–49.

Mesulam, M., Geula, C. *et al.* (**1988**). Nucleus basalis (Ch4) and cortical cholinergic innervation in the human brain: observations based on the distribution of acetylcholinesterase and choline acetyltransferase. *Journal of Comparative Neurology*, 275:216–240.

Mesulam, M., Mufson, E., Wainer, B. & Levey, A. (**1983**a). Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1–Ch6). *Neuroscience*, 10:1185–1201.

Mesulam, M., Mufson, E. J., Levey, A. I., Wainer, B. H. *et al.* (**1983**b). Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. *Journal of Comparative Neurology*, 214:170–197.

Miller, B. T. & D'Esposito, M. (2005). Searching for "the top" in top-down control. *Neuron*, 48:535–538.

Miller, E. K. & Desimone, R. (1994). Parallel neuronal mechanisms for short-term memory. *Science*, 263:520–522.

Miller, G., Galanter, E. & Pribram, K. H. (1960). Plans and the structure of behavior. Holt, Rinehart and Winston, New York.

Miller, G. A. (1956). The magical number seven, plus or minus two: some limits on our capacity for processing information. *Psychological review*, 63:81–97.

Miller, M. H. & Orbach, J. (1972). Retention of spatial alternation following frontal lobe resections in stump-tailed macaques. *Neuropsychologia*, 10:291–298.

Mishkin, M., Ungerleider, L. G. & Macko, K. A. (1983). Object vision and spatial vision: two cortical pathways. *Trends in neurosciences*, 6:414–417.

Mitchell, A. S., Sherman, S. M., Sommer, M. A., Mair, R. G., Vertes, R. P. & Chudasama, Y. (2014). Advances in understanding mechanisms of thalamic relays in cognition and behavior. *The Journal of Neuroscience*, 34:15340–15346.

Mitsis, E. M., Cosgrove, K. P., Staley, J. K., Bois, F., Frohlich, E. B., Tamagnan, G. D., Estok, K. M., Seibyl, J. P. & van Dyck, C. H. (2009). Age-related decline in nicotinic receptor availability with [123I] 5-IA-85380 SPECT. *Neurobiology of aging*, 30:1490–1497.

Morcom, A. M., Good, C. D., Frackowiak, R. S. & Rugg, M. D. (2003). Age effects on the neural correlates of successful memory encoding. *Brain*, 126:213–229.

Motter, B. C. (1994). Neural correlates of feature selective memory and pop-out in extrastriate area V4. *The Journal of neuroscience*, 14:2190–2199.

Müller, N. G., Donner, T. H., Bartelt, O. A., Brandt, S. A., Villringer, A. & Kleinschmidt, A. (**2003**). The functional neuroanatomy of visual conjunction search: a parametric fMRI study. *Neuroimage*, 20:1578–1590.

Müller, N. G. & Ebeling, D. (**2008**). Attention-modulated activity in visual cortex — More than a simple 'spotlight'. *Neuroimage*, 40:818–827.

Müller, N. G. & Kleinschmidt, A. (**2004**). The attentional 'spotlight's' penumbra: center-surround modulation in striate cortex. *Neuroreport*, 15:977–980.

Müller, N. G., Mollenhauer, M., Rösler, A. & Kleinschmidt, A. (**2005**). The attentional field has a Mexican hat distribution. *Vision research*, 45:1129–1137.

Murphy, P. & Sillito, A. (**1991**). Cholinergic enhancement of direction selectivity in the visual cortex of the cat. *Neuroscience*, 40:13–20.

Neisser, U. (**1969**). Selective reading: a method for the study of visual attention. *19th International Congress of Psychology, London.*

Neves, S. R., Ram, P. T. & Iyengar, R. (**2002**). G protein pathways. *Science*, 296:1636–1639.

Nielson, K. A., Langenecker, S. A. & Garavan, H. (**2002**). Differences in the functional neuroanatomy of inhibitory control across the adult life span. *Psychology and aging*, 17:56–71.

Noesselt, T., Hillyard, S. A., Woldorff, M. G., Schoenfeld, A., Hagner, T., Jäncke, L., Tempelmann, C., Hinrichs, H. & Heinze, H.-J. (**2002**). Delayed striate cortical activation during spatial attention. *Neuron*, 35:575–587.

O'Craven, K. M., Downing, P. E. & Kanwisher, N. (**1999**). fMRI evidence for objects as the units of attentional selection. *Nature*, 401:584–587.

Ogawa, S., Lee, T.-M., Kay, A. R. & Tank, D. W. (**1990**). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences*, 87:9868–9872.

Oksama, L. & Hyönä, J. (**2004**). Is multiple object tracking carried out automatically by an early vision mechanism independent of higher-order cognition? An individual difference approach. *Visual cognition*, 11:631–671.

Olivers, C. N., Meijer, F. & Theeuwes, J. (**2006**). Feature-based memory-driven attentional capture: visual working memory content affects visual attention. *Journal of Experimental Psychology: Human Perception and Performance*, 32:1243–1265.

Olsen, R. K., Nichols, E. A., Chen, J., Hunt, J. F., Glover, G. H., Gabrieli, J. D. & Wagner, A. D. (**2009**). Performance-related sustained and anticipatory activity in human medial temporal lobe during delayed match-to-sample. *The Journal of Neuroscience*, 29:11880–11890.

Olson, I. R., Moore, K. S., Stark, M. & Chatterjee, A. (**2006**). Visual working memory is impaired when the medial temporal lobe is damaged. *Journal of cognitive neuroscience*, 18:1087–1097.

Onur, Ö. A., Piefke, M., Lie, C.-H., Thiel, C. M. & Fink, G. R. (**2011**). Modulatory effects of levodopa on cognitive control in young but not in older subjects: a pharmacological fMRI study. *Journal of cognitive neuroscience*, 23:2797–2810.

Pan, K. & Eriksen, C. W. (**1993**). Attentional distribution in the visual field during same-different judgments as assessed by response competition. *Perception & Psychophysics*, 53:134–144.

Parasuraman, R., Greenwood, P. M., Kumar, R. & Fossella, J. (**2005**). Beyond heritability neurotransmitter genes differentially modulate visuospatial attention and working memory. *Psychological Science*, 16:200–207.

Pashler, H. (**1988**). Familiarity and visual change detection. *Perception & psychophysics*, 44:369–378.

Payer, D., Marshuetz, C., Sutton, B., Hebrank, A., Welsh, R. C. & Park, D. C. (**2006**). Decreased neural specialization in old adults on a working memory task. *Neuroreport*, 17:487–491.

Perry, E., Walker, M., Grace, J. & Perry, R. (**1999**). Acetylcholine in mind: a neurotransmitter correlate of consciousness? *Trends in neurosciences*, 22:273–280.

Perry, E. K., Tomlinson, B. E., Blessed, G., Bergmann, K., Gibson, P. H. & Perry, R. H. (**1978**). Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *British Medical Journal*, 2:1457–1459.

Pessoa, L., Kastner, S. & Ungerleider, L. G. (**2003**). Neuroimaging studies of attention: from modulation of sensory processing to top-down control. *The Journal of Neuroscience*, 23:3990–3998.

Pessoa, L. & Ungerleider, L. G. (**2004**). Top-down mechanisms for working memory and attentional processes. In The cognitive neurosciences. MIT Press, Cambridge, 919–930.

Phillips, W. (**1974**). On the distinction between sensory storage and short-term visual memory. *Perception & Psychophysics*, 16:283–290.

Pillon, B., Czernecki, V. & Dubois, B. (**2003**). Dopamine and cognitive function. *Current opinion in neurology*, 16:17–22.

Pollmann, S. & von Cramon, D. Y. (**2000**). Object working memory and visuospatial processing: functional neuroanatomy analyzed by event-related fMRI. *Experimental Brain Research*, 133:12–22.

Posner, M. I. (**1980**). Orienting of attention. *Quarterly journal of experimental psychology*, 32:3–25.

Postle, B. (**2005**). Delay-period activity in the prefrontal cortex: one function is sensory gating. *Cognitive Neuroscience, Journal of*, 17:1679–1690.

Pouget, A. & Driver, J. (**2000**). Relating unilateral neglect to the neural coding of space. *Current opinion in neurobiology*, 10:242–249.

Pylyshyn, Z. W. & Storm, R. W. (**1988**). Tracking multiple independent targets: Evidence for a parallel tracking mechanism. *Spatial vision*, 3:179–197.

Raabe, M., Fischer, V., Bernhardt, D. & Greenlee, M. W. (**2013**). Neural correlates of spatial working memory load in a delayed match-to-sample saccade task. *Neuroimage*, 71:84–91.

Rabbitt, P. (**1979**). How old and young subjects monitor and control responses for accuracy and speed. *British Journal of Psychology*, 70:305–311.

Raedler, T., Bymaster, F., Tandon, R., Copolov, D. & Dean, B. (**2006**). Towards a muscarinic hypothesis of schizophrenia. *Molecular psychiatry*, 12:232–246.

Ranganath, C., DeGutis, J. & D'Esposito, M. (**2004**). Category-specific modulation of inferior temporal activity during working memory encoding and maintenance. *Cognitive Brain Research*, 20:37–45.

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., Dahle, C., Gerstorf, D. & Acker, J. D. (**2005**). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cerebral cortex*, 15:1676–1689.

Raz, N. & Rodrigue, K. M. (**2006**). Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neuroscience & Biobehavioral Reviews*, 30:730–748.

Reinvang, I., Lundervold, A. J., Rootwelt, H., Wehling, E. & Espeseth, T. (**2009**). Individual variation in a cholinergic receptor gene modulates attention. *Neuroscience letters*, 453:131–134.

Reuter-Lorenz, P. A. & Cappell, K. A. (**2008**). Neurocognitive aging and the compensation hypothesis. *Current directions in psychological science*, 17:177–182.

Reuter-Lorenz, P. A., Jonides, J., Smith, E. E., Hartley, A., Miller, A., Marshuetz, C. & Koeppe, R. A. (**2000**). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *Journal of cognitive neuroscience*, 12:174–187.

Ricciardi, E., Handjaras, G., Bernardi, G., Pietrini, P. & Furey, M. L. (**2013**). Cholinergic enhancement reduces functional connectivity and BOLD variability in visual extrastriate cortex during selective attention. *Neuropharmacology*, 64:305–313.

Rieckmann, A., Karlsson, S., Fischer, H. & Bäckman, L. (**2011**). Caudate dopamine D1 receptor density is associated with individual differences in frontoparietal connectivity during working memory. *The Journal of Neuroscience*, 31:14284–14290.

Riggall, A. C. & Postle, B. R. (**2012**). The relationship between working memory storage and elevated activity as measured with functional magnetic resonance imaging. *The Journal of Neuroscience*, 32:12990–12998.

Robbins, T. & Roberts, A. (**2007**). Differential regulation of fronto-executive function by the monoamines and acetylcholine. *Cerebral Cortex*, 17:151–160.

Rorden, C. & Brett, M. (**2000**). Stereotaxic display of brain lesions. *Behavioural neurology*, 12:191–200.

Rottschy, C., Langner, R., Dogan, I., Reetz, K., Laird, A. R., Schulz, J. B., Fox, P. T. & Eickhoff, S. B. (**2012**). Modelling neural correlates of working memory: a coordinate-based meta-analysis. *Neuroimage*, 60:830–846.

Rouder, J. N., Morey, R. D., Morey, C. C. & Cowan, N. (**2011**). How to measure working memory capacity in the change detection paradigm. *Psychonomic Bulletin & Review*, 18:324–330.

Ruff, C. C. (**2013**). Sensory processing: who's in (top-down) control? *Annals of the New York Academy of Sciences*, 1296:88–107.

Saenz, M., Buracas, G. T. & Boynton, G. M. (**2002**). Global effects of feature-based attention in human visual cortex. *Nature neuroscience*, 5:631–632.

Saenz, M., Buraĉas, G. T. & Boynton, G. M. (**2003**). Global feature-based attention for motion and color. *Vision research*, 43:629–637.

Sander, M. C., Werkle-Bergner, M. & Lindenberger, U. (**2011**). Binding and strategic selection in working memory: A lifespan dissociation. *Psychology and aging*, 26:612–624.

Sapir, A., Soroker, N., Berger, A. & Henik, A. (**1999**). Inhibition of return in spatial attention: direct evidence for collicular generation. *Nature Neuroscience*, 2:1053–1054.

Sawaguchi, T. & Goldman-Rakic, P. S. (**1991**). D1 dopamine receptors in prefrontal cortex: involvement in working memory. *Science*, 251:947–950.

Sawaguchi, T. & Goldman-Rakic, P. S. (**1994**). The role of D1-dopamine receptor in working memory: local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. *Journal of Neurophysiology*, 71:515–515.

Schiavetto, A., Köhler, S., Grady, C. L., Winocur, G. & Moscovitch, M. (**2002**). Neural correlates of memory for object identity and object location: effects of aging. *Neuropsychologia*, 40:1428–1442.

Schliebs, R. & Arendt, T. (**2011**). The cholinergic system in aging and neuronal degeneration. *Behavioural brain research*, 221:555–563.

Schneider-Garces, N. J., Gordon, B. A., Brumback-Peltz, C. R., Shin, E., Lee, Y., Sutton, B. P., Maclin, E. L., Gratton, G. & Fabiani, M. (**2010**). Span, CRUNCH, and beyond: working memory capacity and the aging brain. *Journal of cognitive neuroscience*, 22:655–669.

Scholl, B. J. (**2001**). Objects and attention: The state of the art. *Cognition*, 80:1–46.

Schon, K., Hasselmo, M. E., LoPresti, M. L., Tricarico, M. D. & Stern, C. E. (**2004**). Persistence of parahippocampal representation in the absence of stimulus input enhances long-term encoding: a functional magnetic resonance imaging study of subsequent memory after a delayed match-to-sample task. *The Journal of neuroscience*, 24:11088–11097.

Seamans, J. K. & Yang, C. R. (**2004**). The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Progress in neurobiology*, 74:1–58.

Sears, C. R. & Pylyshyn, Z. W. (**2000**). Multiple object tracking and attentional processing. *Canadian Journal of Experimental Psychology*, 54:1–14.

Seppi, K. & Schocke, M. F. (**2005**). An update on conventional and advanced magnetic resonance imaging techniques in the differential diagnosis of neurodegenerative parkinsonism. *Current opinion in neurology*, 18:370–375.

Serences, J. T., Yantis, S., Culberson, A. & Awh, E. (**2004**). Preparatory activity in visual cortex indexes distractor suppression during covert spatial orienting. *Journal of Neurophysiology*, 92:3538–3545.

Shafritz, K. M., Gore, J. C. & Marois, R. (**2002**). The role of the parietal cortex in visual feature binding. *Proceedings of the National Academy of Sciences*, 99:10917–10922.

Sheremata, S. L., Bettencourt, K. C. & Somers, D. C. (**2010**). Hemispheric asymmetry in visuotopic posterior parietal cortex emerges with visual short-term memory load. *The Journal of Neuroscience*, 30:12581–12588.

Shulman, G. L., d'Avossa, G., Tansy, A. P. & Corbetta, M. (**2002**). Two attentional processes in the parietal lobe. *Cerebral Cortex*, 12:1124–1131.

Shulman, G. L., McAvoy, M. P., Cowan, M. C., Astafiev, S. V., Tansy, A. P., d'Avossa, G. & Corbetta, M. (**2003**). Quantitative analysis of attention and detection signals during visual search. *Journal of Neurophysiology*, 90:3384–3397.

Sibley, D. R. & Monsma Jr, F. J. (**1992**). Molecular biology of dopamine receptors. *Trends in pharmacological sciences*, 13:61–69.

Sillito, A. M. & Kemp, J. A. (**1983**). Cholinergic modulation of the functional organization of the cat visual cortex. *Brain research*, 289:143–155.

Silver, M. A. & Kastner, S. (**2009**). Topographic maps in human frontal and parietal cortex. *Trends in cognitive sciences*, 13:488–495.

Silver, M. A., Ress, D. & Heeger, D. J. (**2005**). Topographic maps of visual spatial attention in human parietal cortex. *Journal of neurophysiology*, 94:1358–1371.

Somers, D. C., Dale, A. M., Seiffert, A. E. & Tootell, R. B. (**1999**). Functional MRI reveals spatially specific attentional modulation in human primary visual cortex. *Proceedings of the National Academy of Sciences*, 96:1663–1668.

Soto, D., Heinke, D., Humphreys, G. W. & Blanco, M. J. (**2005**). Early, involuntary top-down guidance of attention from working memory. *Journal of Experimental Psychology: Human Perception and Performance*, 31:248–261.

Soto, D., Humphreys, G. W. & Rotshtein, P. (**2007**). Dissociating the neural mechanisms of memory-based guidance of visual selection. *Proceedings of the National Academy of Sciences*, 104:17186–17191.

Sperling, G. (**1960**). The information available in brief visual presentations. *Psychological monographs: General and applied*, 74:1–29.

Stelzel, C., Basten, U., Montag, C., Reuter, M. & Fiebach, C. J. (**2009**). Effects of dopamine-related gene–gene interactions on working memory component processes. *European Journal of Neuroscience*, 29:1056–1063.

Sternberg, S. (**1963**). Retrieval from recent memory: Some reaction-time experiments and a search theory. *Fourth Annual Meeting of the Psychonomic Society*.

Sternberg, S. (**1966**). High-speed scanning in human memory. *Science*, 153:652–654.

Störmer, V. S., Passow, S., Biesenack, J. & Li, S.-C. (**2012**). Dopaminergic and cholinergic modulations of visual-spatial attention and working memory: Insights from molecular genetic research and implications for adult cognitive development. *Developmental psychology*, 48:875–889.

Sugiura, M., Shah, N., Zilles, K. & Fink, G. (**2005**). Cortical representations of personally familiar objects and places: functional organization of the human posterior cingulate cortex. *Journal of Cognitive Neuroscience*, 17:183–198.

Suhara, T., Fukuda, H., Inoue, O., Itoh, T., Suzuki, K., Yamasaki, T. & Tateno, Y. (**1991**). Age-related changes in human D1 dopamine receptors measured by positron emission tomography. *Psychopharmacology*, 103:41–45.

Sun, H., Yuan, F., Shen, X., Xiong, G. & Wu, J. (**2014**). Role of COMT in ADHD: a systematic meta-analysis. *Molecular neurobiology*, 49:251–261.

Swick, D. & Knight, R. T. (**1998**). Cortical Lesions and Attention. In Attentive Brain. MIT Press, Cambridge, 143–156.

Swisher, J. D., Halko, M. A., Merabet, L. B., McMains, S. A. & Somers, D. C. (**2007**). Visual topography of human intraparietal sulcus. *The Journal of neuroscience*, 27:5326–5337.

Thiel, C. M., Zilles, K. & Fink, G. R. (**2005**). Nicotine modulates reorienting of visuospatial attention and neural activity in human parietal cortex. *Neuropsychopharmacology*, 30:810–820.

Thompson, K. G., Biscoe, K. L. & Sato, T. R. (**2005**). Neuronal basis of covert spatial attention in the frontal eye field. *The Journal of Neuroscience*, 25:9479–9487.

Todd, J. J., Fougnie, D. & Marois, R. (**2005**). Visual short-term memory load suppresses temporo-parietal junction activity and induces inattentional blindness. *Psychological Science*, 16:965–972.

Todd, J. J. & Marois, R. (**2004**). Capacity limit of visual short-term memory in human posterior parietal cortex. *Nature*, 428:751–754.

Todd, J. J. & Marois, R. (**2005**). Posterior parietal cortex activity predicts individual differences in visual short-term memory capacity. *Cognitive, Affective, & Behavioral Neuroscience*, 5:144–155.

Treisman, A. M. (**1960**). Contextual cues in selective listening. *Quarterly Journal of Experimental Psychology*, 12:242–248.

Treue, S. & Trujillo, J. C. M. (**1999**). Feature-based attention influences motion processing gain in macaque visual cortex. *Nature*, 399:575–579.

Tsal, Y. & Benoni, H. (**2010**). Diluting the burden of load: perceptual load effects are simply dilution effects. *Journal of Experimental Psychology: Human Perception and Performance*, 36:1645–1656.

Turchi, J. & Sarter, M. (**1997**). Cortical acetylcholine and processing capacity: effects of cortical cholinergic deafferentation on crossmodal divided attention in rats. *Cognitive Brain Research*, 6:147–158.

Turner, G. R. & Spreng, R. N. (**2012**). Executive functions and neurocognitive aging: dissociable patterns of brain activity. *Neurobiology of aging*, 33:826.e1–826.e13.

Ungerleider, L. & Mishkin, M. (**1982**). Two cortical visual systems. In Analysis of Visual Behavior. MIT Press, Cambridge, 549–586.

Vallar, G. (**1998**). Spatial hemineglect in humans. *Trends in cognitive sciences*, 2:87–97.

Vandenberghe, R., Gitelman, D., Parrish, T. & Mesulam, M. (**2001**). Functional specificity of superior parietal mediation of spatial shifting. *Neuroimage*, 14:661–673.

Vogel, E. K. & Machizawa, M. G. (**2004**). Neural activity predicts individual differences in visual working memory capacity. *Nature*, 428:748–751.

Vogel, E. K., McCollough, A. W. & Machizawa, M. G. (**2005**). Neural measures reveal individual differences in controlling access to working memory. *Nature*, 438:500–503.

Vogel, E. K., Woodman, G. F. & Luck, S. J. (**2001**). Storage of features, conjunctions, and objects in visual working memory. *Journal of Experimental Psychology: Human Perception and Performance*, 27:92–114.

Von Helmholtz, H. (**1867**). Handbuch der physiologischen Optik. Voss, Hamburg.

Voytko, M. L., Olton, D. S., Richardson, R. T., Gorman, L. K., Tobin, J. R. & Price, D. L. (**1994**). Basal forebrain lesions in monkeys disrupt attention but not learning and memory. *The Journal of neuroscience*, 14:167–186.

Wandell, B. A. & Smirnakis, S. M. (**2009**). Plasticity and stability of visual field maps in adult primary visual cortex. *Nature Reviews Neuroscience*, 10:873–884.

Wegener, D., Freiwald, W. A. & Kreiter, A. K. (**2004**). The influence of sustained selective attention on stimulus selectivity in macaque visual area MT. *The Journal of neuroscience*, 24:6106–6114.

Wegener, D., Galashan, F. O., Markowski, D. N. & Kreiter, A. K. (**2006**). Selective visual attention ensures constancy of sensory representations: Testing the influence of perceptual load and spatial competition. *Vision research*, 46:3563–3574.

Wen, X., Yao, L., Liu, Y. & Ding, M. (**2012**). Causal interactions in attention networks predict behavioral performance. *The Journal of Neuroscience*, 32:1284–1292.

Wilken, P. & Ma, W. J. (**2004**). A detection theory account of change detection. *Journal of Vision*, 4:1129–1135.

Wilson, D. E., Muroi, M. & MacLeod, C. M. (**2011**). Dilution, not load, affects distractor processing. *Journal of Experimental Psychology: Human Perception and Performance*, 37:319–335.

Wimber, M., Schott, B. H., Wendler, F., Seidenbecher, C. I., Behnisch, G., Macharadze, T., Bäuml, K. T. & Richardson-Klavehn, A. (**2011**). Prefrontal dopamine and the dynamic control of human long-term memory. *Translational psychiatry*, 1:1–7.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.-O., Nordberg, A., Bäckman, L., Albert, M., Almkvist, O. *et al.* (**2004**). Mild cognitive impairment–beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. *Journal of internal medicine*, 256:240–246.

Winterer, G., Musso, F., Konrad, A., Vucurevic, G., Stoeter, P., Sander, T. & Gallinat, J. (**2007**). Association of attentional network function with exon 5 variations of the CHRNA4 gene. *Human molecular genetics*, 16:2165–2174.

Wojciulik, E. & Kanwisher, N. (**1999**). The generality of parietal involvement in visual attention. *Neuron*, 23:747–764.

Wolff, S. D. & Balaban, R. S. (**1989**). Magnetization transfer contrast (MTC) and tissue water proton relaxation in vivo. *Magnetic resonance in medicine*, 10:135–144.

Wolff, S. D. & Balaban, R. S. (**1994**). Magnetization transfer imaging: practical aspects and clinical applications. *Radiology*, 192:593–599.

Wu, T., Wang, J., Wang, C., Hallett, M., Zang, Y., Wu, X. & Chan, P. (**2012**). Basal ganglia circuits changes in Parkinson's disease patients. *Neuroscience letters*, 524:55–59.

Xu, Y. & Chun, M. M. (**2005**). Dissociable neural mechanisms supporting visual short-term memory for objects. *Nature*, 440:91–95.

Yantis, S., Schwarzbach, J., Serences, J. T., Carlson, R. L., Steinmetz, M. A., Pekar, J. J. & Courtney, S. M. (**2002**). Transient neural activity in human parietal cortex during spatial attention shifts. *Nature neuroscience*, 5:995–1002.

Zhang, W. & Luck, S. J. (**2008**). Discrete fixed-resolution representations in visual working memory. *Nature*, 453:233–235.

Appendix

Statistic tables

Statistic table from chapter 3.4

Table A.1: Means and SEM of performance in the d2 test

	Placebo		Levodopa		Placebo		Galantamine	
	CP (SEM)	ER (SEM)	CP (SEM)	ER (SEM)	CP (SEM)	ER (SEM)	CP (SEM)	ER (SEM)
Young	217.65 (12.29)	13.52 (3.86)	191.95 (16.56)	12.40 (3.43)	227.60 (9.18)	10.06 (3.25)	224.65 (8.33)	10.61 (2.37)
Elderly	146.50 (7.43)	19.15 (3.42)	147.59 (7.60)	18.70 (4.16)	150.29 (7.52)	17.29 (3.07)	150.28 (7.07)	19.16 (7.70)

Statistic tables from chapter 4.1

Table A.2: Main effects of task for each ROI of the filter and memory contrast from the young participants, indicated by F- and p-values

NFHM > HFLM					
Anatomical Structure	**Hemisphere**	**F-Value$_{2,78}$ (p-value)**			
pIPC	R	15.269 (**.000**)			
aIPC	R	10.916 (**.000**)			
Precuneus	R	8.216 (**.001**)			
HFLM > LFHM					
Anatomical Structure	**Hemisphere**	**F-Value$_{2,78}$ (p-value)**	**Anatomical Structure**	**Hemisphere**	**F-Value$_{2,78}$ (p-value)**
Thalamus	R	17.031 (**.000**)	**FEF**	R	24.941 (**.000**)
	R	11.076 (**.000**)	**STC**	L	5.368 (**.007**)
Basal Ganglia (Striatum/Putamen)	R	10.288 (**.000**)	**SPC**	R	20.312 (**.000**)
Thalamus	L	14.721 (**.000**)		R	23.147 (**.000**)
	L	5.624 (**.005**)		R	11.565 (**.000**)
Basal Ganglia (Striatum/Caudate Ncl.)	L	6.777 (**.002**)	**OCC (V3)**	R	15.113 (**.000**)
Basal Ganglia (Pallidum)	L	4.960 (**.009**)	**Fusiform Gyrus**	R	6.374 (**.003**)
Insula	R	13.024 (**.000**)	**Cerebellum**	R	3.818 (**.026**)
	L	7.554 (**.001**)		R	7.680[1] (**.002**)

Note: L = left, R = right
[1] $F_{(2,62)}$

Table A.3: Main effects of task for each ROI of the filter and memory contrast from the elderly participants, indicated by F- and p-values

NFHM>HFLM					
Anatomical Structure	**Hemisphere**	**F-Value$_{2,74}$ (p-value)**			
pIPC	R	28.203 (**.000**)	STC	L	7.287 (**.001**)
aIPC	L	7.427[1] (**.004**)	PHC	R	12.127 (**.000**)
	L	5.716[2] (**.011**)	Cingulate Gyrus	-	6.683 (**.002**)
pTC	R	24.203 (**.000**)			

HFLM>NFHM					
Anatomical Structure	**Hemisphere**	**F-Value$_{2,74}$ (p-value)**	**Anatomical Structure**	**Hemisphere**	**F-Value$_{2,74}$ (p-value)**
Thalamus	R	15.131 (**.000**)	FEF	R	11.371 (**.000**)
Superior colliculus	L	18.514 (**.000**)		R	16.771 (**.000**)
Basal ganglia (Caudate nucleus)	L	13.376 (**.000**)		L	12.655 (**.000**)
Superior colliculus	R	12.408 (**.000**)	pTC	R	8.854 (**.000**)
Thalamus	L	11.713 (**.000**)	SPC	L	10.781 (**.000**)
Caudate nucleus	L	6.133[3] (**.006**)	OCC	R	10.483 (**.000**)
Thalamus	R	4.620 (**.013**)		R	32.684 (**.000**)
Basal ganglia (Caudate nucleus)	R	14.014 (**.000**)		R	22.208 (**.000**)
Lateral Geniculate body	L	5.110 (**.008**)		L	8.602 (**.000**)
Insula	R	33.880 (**.000**)		L	19.986 (**.000**)
	L	38.615 (**.000**)	Cuneus	R	27.234 (**.000**)
IFG	R	18.048 (**.000**)		L	22.312[6] (**.000**)
	L	12.670[4] (**.000**)		R	7.255[7] (**.000**)
SMA	L	15.035[5] (**.000**)			

Note: L = left, R = right
[1] $F_{(1,54)}$ [2] $F_{(1,54)}$ [3] $F_{(2,62)}$ [4] $F_{(2,56)}$ [5] $F_{(2,57)}$ [6] $F_{(2,64)}$ [7] $F_{(2,61)}$

Table A.4: Correlation coefficients and p-values of relation between behavioral performance of young participants in the combined task and effective storage activity

			pIPC R	**aIPC R**	**Precuneus R**
Response Type		**Condition**	**r-value (p-value)**	**r-value (p-value)**	**r-value (p-value)**
Hits	**%**	**NFHM**	-.096 (.560)	.099 (.549)	-.283 (.081)
		LFLM	-.398 (**.012**)	-.238 (.144)	.166 (.311)
		HFLM	-.239 (.143)	-.132 (.422)	.013 (.937)
	ms	**NFHM**	-.022 (.896)	-.237 (.146)	.300 (.063)
		LFLM	-.001 (.996)	-.249 (.126)	.309 (.056)
		HFLM	.002 (.990)	-.216 (.187)	.250 (.125)
Correct rejections	**%**	**LFLM**	.007 (.964)	-.051 (.759)	-.049 (.768)
		HFLM	-.069 (.678)	.427 (**.007**)	.113 (.494)
	ms	**LFLM**	-.086 (.603)	-.291 (.072)	.167 (.310)
		HFLM	-.065 (.695)	-.458 (**.003**)	.166 (.312)
Filter deficit	**Δ%**		-.075 (.650)	-.058 (.726)	.138 (.401)
Memory deficit	**Δ%**		-.123 (.456)	-.226 (.167)	.366 (**.022**)

Table A.5: Correlation coefficients and p-values of relation between behavioral performance of elderly participants in the combined task and effective storage activity in storage related brain regions

Response Type		Condition	pIPC R r-value (p-value)	aIPC L r-value (p-value)	aIPC L r-value (p-value)	pTC R r-value (p-value)	STC L r-value (p-value)	PHC R r-value (p-value)	Cingulate G. r-value (p-value)
Hits	%	NFHM	.270 (.122)	.244 (.164)	.182 (.304)	.098 (.575)	.242 (.162)	.116 (.505)	.183 (.292)
		LFLM	.097 (.587)	.098 (.581)	.062 (.728)	-.042 (.810)	.105 (.550)	.161 (.355)	.139 (.427)
		HFLM	.030 (.865)	.036 (.841)	.023 (.898)	-.084 (.631)	-.144 (.410)	.008 (.964)	.004 (.984)
	ms	NFHM	-.156 (.380)	-.065 (.716)	-.045 (.801)	-.171 (.326)	.013 (.943)	-.299 (.082)	-.054 (.758)
		LFLM	-.168 (.341)	-.203 (.250)	-.211 (.230)	-.080 (.648)	-.073 (.676)	-.227 (.189)	-.094 (.592)
		HFLM	-.209 (.235)	-.250 (.154)	-.136 (.443)	-.179 (.303)	-.023 (.895)	-.267 (.121)	-.060 (.732)
Correct rejections	%	LFLM	.169 (.348)	.259 (.146)	.297 (.093)	.160 (.365)	-.014 (.937)	.304 (.080)	.228 (.194)
		HFLM	-.260 (.144)	.218 (.223)	.428 (**.013**)	-.104 (.560)	-.045 (.801)	-.259 (.139)	.109 (.539)
	ms	LFLM	-.151 (.393)	-.229 (.194)	-.242 (.168)	-.059 (.737)	-.050 (.775)	-.287 (.094)	-.036 (.839)
		HFLM	-.196 (.267)	-.369 (**.032**)	-.363 (**.035**)	-.080 (.646)	-.074 (.672)	-.210 (.225)	-.135 (.438)
Filter deficit	Δ%		.060 (.737)	.056 (.755)	.035 (.846)	.047 (.789)	.247 (.153)	.144 (.409)	.127 (.466)
Memory deficit	Δ%		-.212 (.228)	-.181 (.306)	-.146 (.411)	-.138 (.435)	-.138 (.435)	.078 (.662)	-.076 (.667)

Table A.6: Correlation coefficients and p-values of relation between MT ratio and volume [10^3 mm^3] of substantia nigra and basal forebrain and performance in the combined task in young and elderly participants

			Young			Elderly		
			Substantia Nigra		Basal Forebrain	Substantia Nigra		Basal Forebrain
Response Type		Condition	Volume r-value (p-value)	MT Ratio r-value (p-value)	Volume r-value (p-value)	Volume r-value (p-value)	MT Ratio r-value (p-value)	Volume r-value (p-value)
Hits	%	NFHM	.225 (.174)	-.080 (.632)	.243 (.142)	.042 (.820)	-.168 (.358)	.235 (.181)
		LFLM	-.206 (.215)	-.070 (.675)	-.039 (.816)	-.014 (.940)	-.450 (**.010**)	.317 (.067)
		HFLM	-.147 (.380)	-.104 (.536)	.049 (.769)	-.241 (.184)	-.131 (.476)	.122 (.493)
	ms	NFHM	-.059 (.725)	-.009 (.958)	-.164 (.326)	-.110 (.550)	.117 (.523)	-.139 (.435)
		LFLM	-.133 (.426)	-.119 (.476)	-.086 (.607)	.116 (.527)	-.173 (.343)	-.169 (.338)
		HFLM	-.053 (.751)	-.031 (.853)	-.058 (.729)	-.010 (.958)	.135 (.461)	-.246 (.161)
Correct rejections	%	LFLM	.059 (.723)	.163 (.327)	-.226 (.172)	-.043 (.816)	-.387 (**.028**)	-.176 (.318)
		HFLM	.079 (.637)	.088 (.599)	-.095 (.569)	.179 (.327)	-.230 (.206)	-.268 (.125)
	ms	LFLM	-.234 (.157)	.061 (.718)	-.087 (.605)	.276 (.126)	.089 (.628)	-.165 (.351)
		HFLM	-.211 (.204)	.107 (.522)	-.147 (.377)	.230 (.206)	-.015 (.937)	-.152 (.390)
Filter deficit	Δ%		-.009 (.955)	.063 (.708)	-.097 (.564)	.228 (.209)	-.296 (.100)	-.181 (.306)
Memory deficit	Δ%		-.334 (**.040**)	-.040 (.811)	-.260 (.115)	-.062 (.738)	-.239 (.188)	.040 (.821)

Statistic tables from chapter 4.2

Table A.7: Comparison of VWM capacity performance groups in young and elderly participants

	Young			Elderly			Young vs. Elderly
	low WMC	high WMC	low vs. high	low WMC	high WMC	low vs. high	low vs. high
Set size	Mean (SEM)	Mean (SEM)	F-value$_{1,37}$ (p-value)	Mean (SEM)	Mean (SEM)	F-value$_{1,36}$ (p-value)	F-value$_{1,36}$ (p-value)
2	1,66 (0,05)	1,89 (0,05)	17.831[1] (.000)	1,61 (0,05)	1,77 (0,05)	3.668[2] (.077)	3.079 (.088)
3	2,23 (0,07)	2,68 (0,07)	25.409 (.000)	1,76 (0,07)	2,22 (0,07)	15.569 (**.000**)	.009 (.926)
4	1,92 (0,09)	2,74 (0,08)	44.999 (.000)	0,92 (0,09)	1,86 (0,09)	60.945 (**.000**)	.344 (.561)
5	2,74 (0,14)	3,49 (0,13)	14.012 (.001)	1,85 (0,14)	2,44 (0,14)	10.451 (**.003**)	2.444 (.127)
6	2,69 (0,24)	3,92 (0,23)	15.715 (.000)	1,81 (0,24)	2,25 (0,24)	1.204 (.280)	2.340 (.135)
7	3,04 (0,26)	4,12 (0,25)	8.677 (.006)	1,77 (0,26)	2,39 (0,26)	1.578 (.218)	3.262 (.079)

[1] F(1,26)
[2] F(1,28)

Table A.8: Correlation coefficients and p-values of relation between performance in the combined task and VWM capacity for the group of young and elderly participants

Response Type		Condition	Young r-value (p-value)	Elderly r-value (p-value)
Hits	%	NFHM	.421 (**.008**)	-.188 (.287)
		LFLM	.091 (.580)	-.250 (.155)
		HFLM	.218 (.182)	-.103 (.563)
	ms	NFHM	-.292 (.071)	.479 (**.004**)
		LFLM	-.409 (**.010**)	.387 (**.024**)
		HFLM	-.339 (**.035**)	.434 (**.010**)
Correct rejections	%	LFLM	.099 (.549)	.052 (.770)
		HFLM	.140 (.397)	.292 (.094)
	ms	LFLM	-.250 (.125)	.243 (.167)
		HFLM	-.351 (**.029**)	.220 (.212)
Filter deficit	Δ%		-.184 (.261)	-.135 (.446)
Memory deficit	Δ%		-.359 (**.025**)	-.028 (.875)

Table A.9: Correlation coefficients and p-values of relation between VWM capacity and BOLD response in young

NFHM>HFLM					
Anatomical Structure	**Hemisphere**	**r-value (p-value)**			
pIPC	R	.254 (.114)			
aIPC	R	.060 (.712)			
Precuneus	R	-.089 (.586)			
HFLM>NFHM					
Anatomical Structure	**Hemisphere**	**r-value (p-value)**	**Anatomical Structure**	**Hemisphere**	**r-value (p-value)**
Thalamus	R	-.041 (.803)	FEF	R	-.185 (.253)
	R	.051 (.756)	STC	L	.023 (.890)
Basal Ganglia (Striatum/Putamen)	R	-.034 (.833)	SPC	R	.262 (.103)
Thalamus	L	-.006 (.969)		R	.172 (.289)
	L	.158 (.331)		R	-.007 (.965)
Basal Ganglia (Striatum/Caudate Ncl.)	L	.080 (.625)	OCC (V3)	R	.287 (.073)
Basal Ganglia (Pallidum)	L	.333 (**.036**)	Fusiform Gyrus	R	.277 (.084)
Insula	R	-.042 (.798)	Cerebellum	R	-.150 (.357)
	L	.023 (.890)		R	.136 (.404)

Note: L = left, R = right

Table A.10: Correlation coefficients and p-values of relation between VWM capacity and BOLD response in elderly

NFHM>HFLM					
Anatomical Structure	**Hemisphere**	**r-value (p-value)**	**Anatomical Structure**	**Hemisphere**	**r-value (p-value)**
pIPC	R	-.107 (.534)	STC	L	.329 (**.047**)
aIPC	L	.114 (.510)	PHC	R	-.090 (.597)
aIPC	L	.173 (.312)	Cingulate Gyrus	-	.015 (.932)
pTC	R	-.005 (.976)			
HFLM>NFHM					
Anatomical Structure	**Hemisphere**	**r-value (p-value)**	**Anatomical Structure**	**Hemisphere**	**r-value (p-value)**
Thalamus	R	.213 (.206)	FEF	R	.254 (.129)
Superior colliculus	L	.131 (.438)		R	.195 (.247)
Basal ganglia (Striatum/Caudate ncl.)	L	.226 (.180)		L	.080 (.636)
Superior colliculus	R	.280 (.093)	pTC	R	-.082 (.631)
Thalamus	L	.354 (**.032**)	SPC	L	.130 (.442)
Caudate nucleus	L	.237 (.158)	OCC	R	-.143 (.399)
Thalamus	R	.196 (.246)	OCC/IPC/SPC	R	-.047 (.782)
Basal ganglia (Striatum/Caudate ncl.)	R	.239 (.155)		R	.096 (.574)
Lateral Geniculate body	L	-.131 (.440)		L	.193 (.251)
Insula	R	.007 (.967)		L	-.098 (.564)
	L	-.089 (.599)	Cuneus	R	.376 (**.022**)
IFG	R	-.010 (.954)		L	.116 (.496)
	L	-.099 (.561)		R	-.054 (.751)
SMA	L	.156 (.357)			

Note: L = left, R = right

Statistic tables from chapter 4.3

Table A.11: Effects of levodopa on performance of both age groups in the combined task, indicated by F- and p-values

			Young				
Response Type		Condition	Levodopa Mean (SEM)	Placebo Mean (SEM)	ME Drug $F_{1,18}$ (p-Value)	IE Drug x Task $F_{2,36}$ (p-Value)	IE Drug x Drug Session $F_{1,18}$ (p-Value)
Hits	%	NFHM	78.27 (2.41)	80.10 (1.67)	2.515 (.130)	.269 (.701)[1]	.738 (.402)
		LFLM	89.79 (1.25)	91.98 (0.90)			
		HFLM	87.88 (1.10)	88.26 (1.55)			
	ms	NFHM	872.82 (26.72)	873.72 (25.88)	.580 (.456)	.883 (.422)	7.182 (**.015**)
		LFLM	742.33 (22.59)	752.42(24.59)			
		HFLM	742.77 (24.54)	741.04 (22.35)			
Correct rejections	%	LFLM	97.50 (.617)	98.09 (.50)	.048 (.829)	.101 (.755)	.019 (.893)
		HFLM	92.33 (1.58)	92.17 (1.78)			
	ms	LFLM	742.44 (18.43)	733.07 (15.53)	.014 (.908)	.133 (.719)	18.470 (**.000**)
		HFLM	732.04 (18.17)	726.18 (17.80)			
Filter deficit	Δ%		1.91 (1.31)	3.72 (1.11)	1.149 (.298)	-	.015 (.904)
Memory deficit	Δ%		11.52 (2.65)	11.88 (1.84)	.016 (.902)	-	.001 (.970)

			Elderly				
Response Type		Condition	Levodopa Mean (SEM)	Placebo Mean (SEM)	ME Drug $F_{1,18}$ (p-Value)	IE Drug x Task $F_{2,36}$ (p-Value)	IE Drug x Drug Session $F_{1,18}$ (p-Value)
Hits	%	NFHM	76.46 (2.54)	78.35 (2.19)	1.135 (.301)	1.137 (.332)	3.129 (.094)
		LFLM	87.10 (1.54)	86.98 (1.99)			
		HFLM	82.35 (2.24)	86.11 (2.13)			
	ms	NFHM	1235.28 (37.68)	1238.41 (46.92)	1.425 (.248)	1.491 (.239)	8.550 (**.009**)
		LFLM	1099.24 (35.80)	1071.79 (33.48)			
		HFLM	1065.44 (35.23)	1036.13 (37.43)			
Correct rejections	%	LFLM	98.28 (.81)	98.27 (.56)	1.409 (.251)	.728 (.405)	.969 (.338)
		HFLM	92.68 (1.36)	94.42 (.88)			
	ms	LFLM	1030.79 (28.08)	1053.72 (35.95)	2.586 (.125)	.085 (.774)	26.982 (**.000**)
		HFLM	1039.49 (30.84)	1065.99 (38.03)			
Filter deficit	Δ%		4.75 (1.79)	.88 (1.80)	2.320 (.145)	-	.661 (.427)
Memory deficit	Δ%		10.64 (2.52)	8.63 (2.10)	.570 (.460)	-	.231 (.636)

ME = Main effect
IE = Interaction effect
[1] $F_{2,27}$

Table A.12: Effects of galantamine on performance of both age groups in the combined task indicated by F- and p-values

			Young				
Response Type		Condition	Galantamine Mean (SEM)	Placebo Mean (SEM)	ME Drug $F_{1,18}$ (p-Value)	IE Drug x Task $F_{2,36}$ (p-Value)	IE Drug x Drug Session $F_{1,18}$ (p-Value)
Hits	%	NFHM	80.96 (2.39)	81.63 (2.28)	.205 (.656)	.623 (.542)	.445 (.513)
		LFLM	91.77 (1.39)	90.87 (1.19)			
		HFLM	88.94 (1.36)	87.60 (1.27)			
	ms	NFHM	842.13 (21.10)	833.67 (23.68)	.102 (.753)	.230 (.796)	7.901 (**.012**)
		LFLM	731.85 (20.21)	727.97 (17.89)			
		HFLM	722.89 (19.92)	723.14 (18.15)			
Correct rejections	%	LFLM	97.21 (.75)	98.20 (.59)	.115 (.738)	2.320 (.145)	1.357 (.259)
		HFLM	93.00 (1.66)	91.27 (1.11)			
	ms	LFLM	720.34 (20.77)	712.34 (19.68)	.776 (.390)	.219 (.645)	12.879 (**.002**)
		HFLM	722.15 (23.10)	709.01 (18.35)			
Filter deficit	Δ%		2.83 (1.67)	3.27 (1.20)	.044 (.837)	-	.215 (.649)
Memory deficit	Δ%		10.81 (2.25)	9.24 (2.23)	.697 (.415)	-	.639 (.435)

			Elderly				
Response Type		Condition	Galantamine Mean (SEM)	Placebo Mean (SEM)	ME Drug $F_{1,16}$ (p-Value)	IE Drug x Task $F_{2,32}$ (p-Value)	IE Drug x Drug Session $F_{1,16}$ (p-Value)
Hits	%	NFHM	71.54 (4.24)	73.80 (3.67)	2.570 (.231)	2.022 (.151)	2.596 (.129)
		LFLM	85.03 (2.71)	90.87 (1.19)			
		HFLM	81.02 (3.08)	87.60 (1.27)			
	ms	NFHM	1188.46 (44.10)	1191.67 (45.28)	1.213 (.289)	1.105 (.345)	13.594 (**.002**)
		LFLM	1077.23 (38.57)	1070.98 (46.43)			
		HFLM	1048.51 (45.57)	1018.85 (35.89)			
Correct rejections	%	LFLM	99.03 (.55)	99.44 (.30)	.122 (.732)	.058 (.813)	8.308 (**.012**)
		HFLM	92.52 (1.38)	92.09 (1.25)			
	ms	LFLM	1035.26 (32.54)	1040.61 (37.72)	.413 (.531)	2.088 (.170)	26.543 (**.000**)
		HFLM	1037.71 (37.71)	1067.83 (34.76)			
Filter deficit	Δ%		4.00 (1.77)	4.86 (2.51)	.083 (.778)	-	.001 (.971)
Memory deficit	Δ%		13.50 (2.59)	8.93 (2.07)	2.829 (.115)	-	.235 (.635)

ME = Main effect
IE = Interaction effect

Table A.13: Effects of drug administration (galantamine/levodopa) on performance of both age groups in the combined task in dependency on VWM capacity, indicated by F- and p-values

			Young	
			IE Levodopa x VWM capacity Performance Group	IE Galantamine x VWM capacity Performance Group
Response Type		Condition	F-Value$_{1,15}$ (p-Value)	F-Value$_{1,16}$ (p-Value)
Hits	%	NFHM LFLM HFLM	1.188 (.293)	2.421 (.139)
	ms	NFHM LFLM HFLM	.008 (.931)	.477 (.500)
Correct rejections	%	LFLM HFLM	.209 (654)	.059 (411)
	ms	LFLM HFLM	.086 (774)	.141 (712)
Filter deficit	Δ%		1.918 (.186)	.135 (.718)
Memory deficit	Δ%		.675 (.424)	.289 (.598)

			Elderly	
			IE Levodopa x VWM capacity Performance Group	IE Galantamine x VWM capacity Performance Group
Response Type		Condition	F-Value$_{1,16}$ (p-Value)	F-Value$_{1,13}$ (p-Value)
Hits	%	NFHM LFLM HFLM	.215 (.649)	.020 (.890)
	ms	NFHM LFLM HFLM	2.383 (.142)	.122 (.734)
Correct rejections	%	LFLM HFLM	.069 (.795)	.403 (.538)
	ms	LFLM HFLM	.021 (.888)	.246 (.630)
Filter deficit	Δ%		.323 (.578)	.328 (.578)
Memory deficit	Δ%		1.271 (.276)	.331 (.577)

IE = Interaction effect

Table A.14: Effects of levodopa administration on performance of both age groups in the combined task in dependency on SN_{vol}, SN_{MT} and BF_{vol}, indicated by F- and p-values

			Young		
			IE Levodopa x Substantia Nigra		IE Levodopa x Basal Forebrain
			Volume	MT Ratio	Volume
Response Type		Condition	F-Value$_{1,17}$ (p-Value)	F-Value$_{1,17}$ (p-Value)	F-Value$_{1,17}$ (p-Value)
Hits	%	NFHM	.007 (.932)	.828 (.376)	.029 (.866)
		LFLM			
		HFLM			
	ms	NFHM	.300 (.591)	.164 (.691)	.291 (.596)
		LFLM			
		HFLM			
Correct rejections	%	LFLM	.000 (.988)	.007 (.935)	.033 (.859)
		HFLM			
	ms	LFLM	.061 (.809)	.284 (.601)	.170 (.685)
		HFLM			
Filter deficit	Δ%		2.195 (.157)	.092 (.766)	.245 (.627)
Memory deficit	Δ%		.000 (.985)	.750 (.399)	1.794 (.198)
			Elderly		
			IE Levodopa x Substantia Nigra		IE Levodopa x Basal Forebrain
			Volume	MT Ratio	Volume
Response Type		Condition	F-Value$_{1,16}$ (p-Value)	F-Value$_{1,16}$ (p-Value)	F-Value$_{1,17}$ (p-Value)
Hits	%	NFHM	.118 (.735)	2.323 (.147)	2.279 (.150)
		LFLM			
		HFLM			
	ms	NFHM	2.176 (.160)	.010 (.921)	.510 (.485)
		LFLM			
		HFLM			
Correct rejections	%	LFLM	2.457 (.137)	1.005 (.331)	.628 (.439)
		HFLM			
	ms	LFLM	2.967 (.104)	.129 (.725)	1.226 (.284)
		HFLM			
Filter deficit	Δ%		1.474 (.242)	.814 (.380)	.120 (.733)
Memory deficit	Δ%		1.725 (.208)	.006 (.940)	.625 (.440)

IE = Interaction effect

Table A.15: Effects of galantamine administration on performance of both age groups in the combined task in dependency on SN_{vol}, SN_{MT} and BF_{vol}, indicated by F- and p-values

			Young		
			IE Galantamine x Substantia Nigra		IE Galantamine x Basal Forebrain
			Volume	MT Ratio	Volume
Response Type		Condition	F-Value$_{1,17}$ (p-Value)	F-Value$_{1,17}$ (p-Value)	F-Value$_{1,17}$ (p-Value)
Hits	%	NFHM LFLM HFLM	.162 (.693)	.089 (.769)	.097 (.759)
	ms	NFHM LFLM HFLM	.609 (.446)	.221 (.644)	.760 (.395)
Correct rejections	%	LFLM HFLM	.745 (.400)	.001 (.973)	.194 (.665)
	ms	LFLM HFLM	6.447 (**.021**)	.047 (.831)	1.856 (.191)
Filter deficit	Δ%		1.446 (.246)	.002 (.962)	1.807 (.197)
Memory deficit	Δ%		.640 (.435)	.017 (.898)	1.695 (.210)

			Elderly		
			IE Galantamine x Substantia Nigra		IE Galantamine x Basal Forebrain
			Volume	MT Ratio	Volume
Response Type		Condition	F-Value$_{1,14}$ (p-Value)	F-Value$_{1,14}$ (p-Value)	F-Value$_{1,15}$ (p-Value)
Hits	%	NFHM LFLM HFLM	.078 (.785)	7.034 (**.021**)	.003 (.959)
	ms	NFHM LFLM HFLM	3.775 (.076)	.418 (.530)	3.347 (.090)
Correct rejections	%	LFLM HFLM	.054 (.820)	13.093 (**.004**)	1.670 (.219)
	ms	LFLM HFLM	.089 (.771)	1.812 (.203)	.540 (.475)
Filter deficit	Δ%		1.096 (.316)	2.400 (.147)	6.063 (**.029**)
Memory deficit	Δ%		.047 (.831)	.098 (.760)	4.453 (.052)

IE = Interaction effect

Statistic tables from chapter 4.4

Table A.16: Main Effects of DBH polymorphisms on performance in the combined task in young and elderly participants reflected in F- and p-values

Response Type		Condition	Young		Elderly	
			ME DBH	IE DBH x Task	ME DBH	IE DBH x Task
			F-value$_{2,33}$ (p-value)	F-value$_{4,66}$ (p-value)	F-value$_{2,30}$ (p-value)	F-value$_{4,60}$ (p-value)
Hits	%	NFHM LFLM HFLM	.225 (.800)	.268 (.897)	2.904 (.071)	.970 (.431)
	ms	NFHM LFLM HFLM	2.490 (.098)	1.085 (.371)	1.474 (.246)	.146 (.964)
Correct rejections	%	LFLM HFLM	2.813 (.074)	2.145 (.133)	.269 (.767)	.081 (.922)
	ms	LFLM HFLM	.767 (.473)	1.976 (.155)	.032 (.969)	1.031 (.370)
Filter deficit	Δ%		.090 (.914)	-	.340 (.715)	-
Memory deficit	Δ%		4.011 (.053)	-	1.056 (.361)	-

ME = Main effect
IE = Interaction effect

Table A.17: Main Effects of COMT polymorphisms on performance in the combined task in young and elderly participants reflected in F- and p-values

Response Type		Condition	Young		Elderly	
			ME COMT	IE COMT x Task	ME COMT	IE COMT x Task
			F-value$_{2,34}$ (p-value)	F-value$_{4,68}$ (p-value)	F-value$_{2,30}$ (p-value)	F-value$_{4,60}$ (p-value)
Hits	%	NFHM LFLM HFLM	2.128 (.135)	1.529 (.204)	.592 (.560)	.208 (.933)
	ms	NFHM LFLM HFLM	2.936 (.067)	.823 (.515)	.622 (.544)	1.117 (.358)
Correct rejections	%	LFLM HFLM	1.670 (.203)	.431 (.653)	2.242 (.129)	1.001 (.383)
	ms	LFLM HFLM	.583 (.564)	2.345 (.111)	1.476 (.246)	.046 (.955)
Filter deficit	Δ%		.028 (.972)	-	.012 (.988)	-
Memory deficit	Δ%		1.510 (.235)	-	.285 (.754)	-

ME = Main effect
IE = Interaction effect

Table A.18: Main Effects of CHRNA4 polymorphisms on performance in the combined task in young and elderly participants reflected in F- and p-values

Response Type		Condition	Young		Elderly	
			ME CHRNA4	IE CHRNA4 x Task	ME CHRNA4	IE CHRNA4 x Task
			$F\text{-value}_{2,33}$ (p-value)	$F\text{-value}_{4,66}$ (p-value)	$F\text{-value}_{2,29}$ (p-value)	$F\text{-value}_{4,58}$ (p-value)
Hits	%	NFHM LFLM HFLM	1.148 (.330)	.331 (.856)	.318 (.730)	.311 (.869)
	ms	NFHM LFLM HFLM	.144 (.867)	1.691 (.163)	.768 (.474)	.826 (.514)
Correct rejections	%	LFLM HFLM	1.030 (.368)	.223 (.801)	3.252 (.059)	1.641 (.218)
	ms	LFLM HFLM	.738 (.486)	2.368 (.109)	.343 (.712)	.608 (.552)
Filter deficit	Δ%		.555 (.579)	-	.121 (.887)	-
Memory deficit	Δ%		.421 (.660)	-	.493 (.616)	-

ME = Main effect
IE = Interaction effect
[1] F(2,23)

Table A.19: Effects of DBH, COMT and CHRNA4 polymorphisms in dependency of age on performance in the combined task in young and elderly participants reflected in F- and p-values

Response Type		Condition	Young vs. Elderly		
			IE DBH x age	IE COMT x age	IE CHRNA4 x age
			$F\text{-value}_{2,63}$ (p-value)	$F\text{-value}_{2,64}$ (p-value)	$F\text{-value}_{2,62}$ (p-value)
Hits	%	NFHM LFLM HFLM	2.397 (.100)	.034 (.967)	.014 (.986)
	ms	NFHM LFLM HFLM	.644 (.529)	1.100 (.339)	.590 (.557)
Correct rejections	%	LFLM HFLM	.909 (.409)	2.969 (.060)	.941 (.397)
	ms	LFLM HFLM	.137 (.872)	1.781 (.177)	.003 (.997)
Filter deficit	Δ%		.485 (.618)	.008 (.992)	.346 (.709)
Memory deficit	Δ%		1.041 (.359)	.821 (.445)	.864 (.427)

IE = interaction effect

Danksagung

Mein Doktorvater sagte einmal: "'Die Höhen und Tiefen gehören zur Promotion dazu, aber die Ausschläge nehmen mit der Zeit ab!"'. Nach vielen Jahren intensiver Arbeit möchte ich mich bei den Menschen bedanken, die mich in dieser Zeit durch alle Höhen und Tiefen begleitet und unterstützt haben.

Zunächst möchte ich mich bei meinem Doktorvater Prof. Dr. Notger Müller bedanken, der mir die Promotion ermöglichte und mir immer mit seinem Fachwissen zur Seite stand.

Ein großer Dank gilt Prof. Dr. Ariel Schönfeld und Prof. Dr. Max Hopf für die fachliche und moralische Unterstützung, besonders zu Beginn der Promotion. An dieser Stelle möchte ich auch Hendrik Strumpf für die Starthilfe beim Programmieren und die Engelsgeduld danken. Ein Weiterer Dank gilt Christian Merkel, meinem persönlichen Statistikberater, der immer ein offenes Ohr (nicht nur für fachliche Fragen) hatte und mir in dieser Zeit als guter Freund ans Herz gewachsen ist.

Ein besonderer Dank gilt auch den MTAs Renate Blobel, Denise Scheerman, Ilona Wiedenhöft und Kerstin Möhring für die angenehme Gesellschaft während der unzähligen Messstunden am MRT. Dank ihrer Unterstützung konnte ich, nicht nur messbedingte Probleme, aller Art bewältigen. In diesem Zuge möchte ich auch den MTAs am DZNE, Franziska Schulze und Christin Ruß, für die unkomplizierte Unterstützung bei der Blutabnahme danken. Ebenso möchte ich Marlen Schmicker und Melanie Schwefel erwähnen, die mir bei der Probandenrekrutierung eine tatkräftige Unterstützung waren.

Ebenfalls bin ich allen Messärzten und Probanden, die sich für die vielen Messstunden zur Verfügung gestellt haben, zu Dank verpflichtet.
Für die angenehme und freundschaftliche Atmosphäre danke ich meiner Arbeitsgruppe, der AG Neuroprotektion. Insbesondere möchte ich mich bei Andreas Becke bedanken, der mir das Gefühl für Daten beigebracht und mich fachlich Unterstützt hat.
Für die Motivation, gerade in den schweren Phasen der Promotion, und den tollen Zusammenhalt möchte mich bei meinen Berliner Klassenkameraden der Graduiertenschule "'Berlin School of Mind and Brain"' bedanken.
Ein großer Dank gilt auch Katrin Klemm und Dr. Sören Wenzel, die mir zu den Seminarzeiten in Berlin ein zweites Zuhause gegeben haben.
Ein riesiger Dank gilt meinen Eltern Ute und Gerhard Vellage, die in jeglicher Hinsicht die Grundsteine für meinen Weg gelegt haben und mir für diesen Weg sowohl Wurzeln als auch Flügel mitgegeben haben.
Nicht zuletzt möchte ich Thomas Klein danken, der mich in meiner Arbeit bestärkt hat, wenn ich an mir gezweifelt habe und mir gezeigt hat, die Dinge nicht immer zu Ernst zu sehen.

Curriculum vitae

Der Lebenslauf wird aus Gründen des Datenschutzes in der elektronischen Fassung dieser Arbeit nicht veröffentlicht.

Publikationen

The contribution of Acetylcholine and Dopamine to subprocesses of visual Working Memory - what Patients with amnestic Mild Cognitive Impairment and Parkinson's disease can tell us

Joana Blatt, ***Anne-Katrin Vellage***, Bernhard Baier, Notger G. Müller

Neuropsychologia. 2014., 61: pp. 89-95

Neural sources of visual working memory maintenance in human parietal and ventral extrastriate visual cortex

Andreas Becke, Notger G. Müller, ***Anne-Katrin Vellage***, Ariel Schönfeld, Jens-Max Hopf

NeuroImage. 2015., 110: pp. 78-86

Selbstständigkeitserklärung

Dipl. Biol. Anne-Katrin Vellage
Deutsches Zentrum für Neurodegenrative Erkrankungen (DZNE)
Leipzigerstrasse 44
39120 Magdeburg
03 91/67 24 52 2
anne-katrin.vellage@dzne.de

Hiermit erkläre ich, Anne-Katrin Vellage, dass ich die von mir eingereichte Dissertation zu dem Thema:

Role of Neurotransmitter Dopamine and Acetylcholine during the Interaction of Working Memory and Selective Attention

selbstständig verfasst, nicht schon als Dissertation verwendet und nur unter Benutzung der angegebenen Quellen und technischen Hilfen angefertigt habe.
Weiterhin erkläre ich, dass ich weder diese noch eine andere Arbeit zur Erlangung des akademischen Grades doctor rerum naturalium (Dr. rer. nat.) an anderen Einrichtungen eingereicht habe.

Magdeburg, den 24. Juni 2015

Dipl. Biol. Anne-Katrin Vellage