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Neural and psychological mechanisms of cognitive training in older adults

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Abstract

Age-related cognitive decline and alterations in the dopaminergic system are well described phenomena of healthy aging. However, the relation between structural or systemic changes and cognition remains unclear. Moreover, it is yet an open question whether cognitive performance in older adults can be improved by cognitive training. Within the scope of this thesis, 83 healthy older participants were recruited for a cognitive training study. Structural MRI and a broad cognitive assessment tapping on fluid and crystallized intelligence, verbal and numeric memory, processing speed, and executive functioning were performed before and after the training. MRI data were analyzed with respect to grey matter changes using voxel-based morphometry as well as myelin (MT) and iron (R2*) markers using voxel-based quantification. First, data of the initial measurement were analyzed by correlating structural parameters of the basal ganglia and the SN/VTA with age and cognitive performance (study 1). An age-related decline of grey matter and myelin, and an increase of iron were revealed. Moreover, increased iron levels and demyelination predicted performance in verbal memory and executive functioning. Within the SN/VTA, age-related demyelination was detected. In a next step, the data of the cognitive training study were analyzed (study 2). Since novelty processing can boost dopamine release which supports long-term memory, a novelty manipulation was included in the training. Two groups completed a 4-week working memory training (i.e., 2-back task), either in combination with novel or familiarized nature movies, while a third group did not receive any training. Task specific improvements in working memory and reaction time, but no transfer or novelty-related improvements to other cognitive domains were observed. At the neural level, no significant structural changes were detected in either group. To investigate whether novelty improves recollection memory in a younger sample (N=182), novelty was tested at three time points: 15 min before, directly after, and 15 minutes after encoding of a word list (study 3). However, no effects of novelty could be revealed at any time point. The findings provide new insights into micro- and macrostructural characteristics of healthy aging and underline the link between cognition and structural integrity. Further, we suggest that cognitive training benefits are restricted to the trained task and that passive exposure to novelty is not sufficient to promote dopaminergic neuromodulation.

German Abstract/ Deutsche Zusammenfassung

Altersbedingte kognitive Beeinträchtigungen und Veränderungen des dopaminergen Systems sind ein gut beschriebenes Phänomen gesunden Alterns. Die Beziehung zwischen strukturellen bzw. systemischen Änderungen und Kognition bleibt jedoch unklar. Des Weiteren ist fraglich, ob kognitive Trainings die kognitive Leistung im Alter verbessern können. Im Zuge dieser Dissertation wurden 83 gesunde, ältere Probanden für eine kognitive Trainingsstudie rekrutiert. Strukturelles MRT sowie eine umfangreiche kognitive Diagnostik, welche Bereiche der fluiden und kristallinen Intelligenz, des verbalen und numerischen Gedächtnisses, der Verarbeitungsgeschwindigkeit und Exekutivfunktionen einschloss, wurden vor und nach dem Training durchgeführt. Graue Substanz wurde anhand voxel-basierter Morphometrie, und Marker für Myelin und Eisen (MT bzw. R2*) anhand voxel-basierter Quantifikation gemessen. Zuerst wurden die Daten der ersten Erhebung analysiert und Parameter der strukturellen Integrität der Basalganglien sowie der SN/VTA mit Alter und kognitiver Leistung korreliert (Studie 1). Es zeigten sich ein altersbedingter Abbau grauer Substanz und Myelin sowie ein Anstieg an Eisen. Zudem waren erhöhte Eisenwerte sowie Demyelinisierung Prädiktoren für die Leistung im verbalen Gedächtnis und der Exekutivfunktionen. Innerhalb der SN/VTA konnte eine altersbedingte Demyelinisierung nachgewiesen werden. Im folgenden Schritt wurden die Daten der Trainingsstudie analysiert (Studie 2). Da die Darbietung von Neuheit zu gedächtnisfördernder Dopaminausschüttung führen kann, wurde eine Neuheits-Manipulation in das Training integriert. Zwei Gruppen führten ein 4-wöchiges kognitives Training einer Arbeitsgedächtnisaufgabe (2-back) durch, entweder kombiniert mit neuen oder bekannten Naturfilmen, während eine dritte Gruppe an keinem Trainingsprogramm teilnahm. Es konnten aufgabenspezifische Verbesserungen in der Arbeitsgedächtnisleistung sowie der Reaktionszeit festgestellt werden, jedoch kein Transfer oder neuheitsinduzierte Verbesserungen auf andere kognitive Domänen. Auf der neuronalen Ebene wurden zudem in keiner der Gruppen signifikante mikro- oder makrostrukturelle Veränderungen beobachtet. Um zu untersuchen, ob Neuheitsexposition in einer jüngeren Altersgruppe (N=182) zu Verbesserungen des Wiedererkennungsgedächtnisses führt, wurde Neuheitsexposition zu drei verschiedenen Zeitpunkten gemessen: 15 Minuten vor, direkt nach und 15 Minuten nach einer

Enkodierungsaufgabe (Studie 3). Es konnte jedoch für keinen der gemessenen Zeitpunkte ein positiver Effekt von Neuheit feststellt werden. Die Ergebnisse liefern neue Einsichten in mikro- und makrostrukturelle Eigenschaften gesunden Alterns und verdeutlichen den Zusammenhang zwischen Kognition und struktureller Integrität. Des Weiteren schlussfolgern wir, dass kognitive Trainingserfolge auf die trainierte Aufgabe beschränkt sind und eine passive Exposition von Neuheit nicht ausreicht, um eine dopaminerge Neuromodulation anzuregen.

Abbreviations

BFI-10	Big-Five inventory
BG	Basal ganglia
BOLD	Blood-oxygen-level-dependent
(c)HR	(Corrected) hit rate
CNS	Central nervous system
CON	Control group
CSF	Cerebrospinal fluid
DA	Dopamine
DARTEL	Diffeomorphic anatomical registration using exponentiated lie algebra
DWI	Diffusion weighted imaging
EEG	Electroencephalography
FA	Fractional anisotropy
FAM	Familiarity group
FDR	False discovery rate
FLASH	Fast low angle shot
(f)MRI	(Functional) magnetic resonance imaging
FWE	Familywise error
FWHM	Full width at half maximum
Gc	Crystallized intelligence
Gf	Fluid intelligence
GM	Grey matter
ICC	Intra class correlation coefficient
LPS 50+	Leistungsprüfsystem 50+
LTM	Long-term memory
LTP	Long-term potentiation
MDBF	Mehrdimensionale Befindlichkeitsfragebogen
MNI	Montreal neurological institute
MoCA	Montreal cognitive assessment
MPM	Multiparameter mapping
MTL	Medial temporal lobe
MT(R)	Magnetization transfer (ratio)

MWT	Mehrfachwahl-Wortschatz-Test
NAcc	Nucleus accumbens
NOV	Novelty group
PD	Proton density
PET	Positron emission tomography
PFC	Prefrontal cortex
PNS	Peripheral nervous system
R2*	Effective transverse relaxation rate
RF	Radio frequency
ROI	Region of interest
RT	Reaction time
SD	Standard deviation
SEM	Standard error of the mean
SN/VTA	Substantia nigra/ventral tegmental area
SPM	Statistical parametric mapping
SVC	Small volume correction
TE	Echo time
TMT	Trail making test
TR	Repetition time
VBM	Voxel-based morphometry
VBQ	Voxel-based quantification
VLMT	Verbaler Lern- und Merkfähigkeitstest
VR	Virtual reality
WHO	World health organization
WM	White matter

Theoretical background

- Cognitive development
- Structural and systemic changes
- Reserve, maintenance, and compensation
- Cognitive training
- Dopaminergic novelty processing
- Research aim

1 Introduction

The World Health Organization (WHO) defines healthy aging as "the process of developing and maintaining the functional ability that enables wellbeing in older age" (WHO | What is Healthy Ageing?). Functional ability in that sense is described as meeting basic needs, learning, making decisions, being mobile, building and maintaining relationships, and to contribute to the society. Therefore, healthy aging does not imply the absence of diseases but rather an adequate coping of age-related restrictions to enable wellbeing.

In the notion that aging is the major risk factor for the development of a degenerative disease (Amaducci and Tesco, 1994), the medical progress which leads to increased life expectancy confronts the society with new challenges. According to the WHO, Alzheimer's disease is the most frequent form of dementia, followed by vascular and frontal types (WHO | Dementia). Importantly, early precursors can precede a manifestation of a neurodegenerative disease years before diagnosed onset. Along the same lines, healthy older adults often report memory decline or impairments of daily life abilities (Reid and Maclullich, 2006; Vestergren and Nilsson, 2011), and research showed that subjective complaints are linked with the risk of future cognitive impairments (Reid and Maclullich, 2006). Yet, the underlying neural link between age-related decline of cognitive performance in healthy older adults and the manifestation of a neurodegenerative disease is an open question. With the goal of maintaining an individual's independence as long as possible, non-pharmacological prevention and intervention programs of age-related cognitive decline are in need. Therefore, it is crucial to investigate the underlying neural mechanisms of healthy aging and to decode which neural substrates lead to differences in performance between healthy older adults. By answering these questions, possible intervention models could be designed, and primary microstructural indicators, which may represent a critical threshold of cognitive impairments, may be addressed. In the following chapters, the theoretical background of age-related cognitive decline, changes in structure and system, reserve mechanisms, and implications of cognitive training are presented. Finally, the outline of the thesis is described.

1.1 Cognitive development

While age-related cognitive decline is a well described phenomenon, inter-individual differences regarding onset, speed, and severity occur. Cognitive aspects which appear to be relatively stable are autobiographical memory (Fromholt et al., 2003; Bauer et al., 2014; Köber et al., 2019), semantic knowledge (Nilsson, 2003; Rönnlund et al., 2005), and emotional functioning (Carstensen et al., 2003), but other abilities record a strong decline. Longitudinal evidence shows that by the age of 50 years onwards, decreases in several cognitive domains, such as inductive reasoning, numeric and verbal abilities, verbal memory, perceptual speed, and spatial orientation can be observed (Schaie, 1996; Hedden and Gabrieli, 2004). Moreover, changes in intelligence have been reported. While fluid intelligence (Gf; e.g., inductive reasoning, figural and semantic relations, associative memory) reaches its peak already at the age of 25, crystallized intelligence (Gc; e.g., verbal comprehension, formal reasoning, experiential evaluation, general reasoning, ideational fluency) has been found being relatively stable until the age of 60 (Horn and Cattell, 1967; Kaufman and Horn, 1996).

1.2 Structural and systemic changes

Cognitive impairments are strongly associated with age-related micro- and macrostructural alterations. Besides numerous processes which undergo age-related changes, this section will focus on grey matter (GM) volume (Brickman et al., 2007), myelin (Peters, 2002), brain iron (Zecca et al., 2004), and the dopaminergic system (Bäckman et al., 2006), specifically in relation to the basal ganglia (BG).

1.2.1 Grey matter volume

GM structure consists of an accumulation of neuronal cell bodies (somata), synapses, and local wiring (i.e., dendrites and unmyelinated axons), and is located in the outer surface of the brain (i.e., cortex) and subcortical areas (e.g., BG). In contrast to GM, white matter (WM) is organized within tracts of (mainly) myelinated axons and transmits information between functional GM networks throughout the brain (Wen and Chklovskii, 2005; Purves, 2008). The BG are a GM structure formed by several nuclei, namely the caudate, putamen, pallidum, and nucleus accumbens (NAcc). The BG together with the substantia nigra/ventral tegmental area (SN/VTA)

build the dopaminergic nigrostriatal pathway (Lanciego et al., 2012; Haber, 2014), and are involved in several cognitive and motor functions (Middleton and Strick, 2000).

With increasing age, changes of neural and dendritic architecture and microstructural damages (Esiri, 2007; Freeman et al., 2008) can cause GM atrophy, which is linked to cognitive decline (Ramanoël et al., 2018), impaired performance in executive functioning (Zimmerman et al., 2006; Laubach et al., 2018), and declines in episodic memory and semantic fluency (Pelletier et al., 2017). Such age-related reductions in GM volume have been reported within the cortex (Draganski et al., 2011; Callaghan et al., 2014), as well as subcortical structures. Within the hippocampus, GM volume loss is strongly linked to Alzheimer's disease (Boutet et al., 2014), but also occurs in healthy adults (Nobis et al., 2019). In addition, age-related GM volume reductions were revealed in the BG (Raz et al., 2007; Callaghan et al., 2014; Steiger et al., 2016), and within the caudate, age-related GM decrease has been associated with impaired memory performance (Bauer et al., 2015).

1.2.2 Myelin

Myelin, which is a white colored isolating tissue among neuronal axons, is mostly found along WM structures, but is also present in GM (Shafee et al., 2015). Within the human organism, two kinds of glia cells are responsible for the myelin production. While Schwann cells produce myelin in the peripheral nervous system (PNS), oligodendrocytes regulate myelin supply in the central nervous system (CNS). Oligodendrocytes are the biggest form of glia cells and functionally connected to the axons on which they promote myelin production (Nave and Werner, 2014). Due to the high conductivity of myelin, myelinated axons promote faster transmission of action potentials compared to unmyelinated axons. However, to ensure that the action potential which is sent along the axon is not attenuated, the axon is not completely myelinated. Several myelinated segments, called internodes, surround the axon, and are separated by unmyelinated segments (Nodes of Ranvier). These contain sodium channels which send the action potentials from one internode to another along the axon (Purves, 2008; Suminaite et al., 2019).

Myelin is strongly associated with learning processes and brain plasticity (Sampaio-Baptista and Johansen-Berg, 2017), but age-related demyelination can lead to a deceleration

of processing speed (Chopra et al., 2018), possibly caused by impaired velocity along the myelin sheaths (Nave and Werner, 2014; Freeman et al., 2016). Age-related decreases of myelin are mostly found in WM structures (e.g., frontal and parietal regions, optic radiations, corpus callosum, corticospinal tract; Draganski et al., 2011; Callaghan et al., 2014), but also occur within cortical and subcortical (i.e., BG) areas (Callaghan et al., 2014; Steiger et al., 2016).

1.2.3 Iron

Within the PNS, iron synthesis and transport are well described, but less is known about iron metabolism within the human brain (Zecca et al., 2004; Mills et al., 2010). Iron intake is mostly related to the production of red blood cells during erythropoiesis within the bone marrow (Winter et al., 2014; Muckenthaler et al., 2017; Singh, 2018), but a small portion of iron crosses the blood brain barrier (Burdo and Connor, 2003). While heme iron is mostly related to the hemoglobin molecule and blood circulation, non-heme iron is present within brain cells (Hallgren and Sourander, 1958; Hametner et al., 2013). Within the brain, iron is mainly stored within oligodendrocytes which require non-heme iron for myelin production (Todorich et al., 2009). Besides myelin production, the non-heme iron enzyme tyrosine hydroxylase (Zecca et al., 2004) is involved in dopamine (DA) synthesis. Hence, brain iron is crucial for numerous metabolic processes. A recent study could show a positive link between longitudinal brain iron development within the BG and cognitive performance in adolescence, alongside with the highest increases of iron being observed in the putamen/pallidum (Larsen et al., 2020).

The sensitivity of iron within the brain is underlined by several neurological conditions. Importantly, reduced as well as increased iron levels can initiate pathological processes. In this view, rodent studies of dietary iron deficiency revealed alterations of the dopaminergic system (Erikson et al., 2001; Bianco et al., 2008; Unger et al., 2008), and decreased iron levels within the striatum were linked to reduced DA receptor density (Erikson et al., 2001). While studies in humans that investigate the lack of iron and its direct impact on dopaminergic neuromodulation are yet lacking, there is at least indirect evidence that even in humans, dopaminergic pathways might be affected by decreases in iron. For instance, infants with iron deficiency show impairments in inhibition control, executive functioning, social-emotional behavior, and motor control, abilities which are strongly linked to alterations of the

dopaminergic system (Lozoff, 2011). Moreover, in infants, iron deficiency has been related to hypomyelination and impaired development (Beard, 2008; Lukowski et al., 2010), underpinning the link between iron and myelin synthesis. The picture changes when iron levels cross a certain threshold and initiate a toxic accumulation. Such findings of increased iron levels have been related to numerous pathological processes. For instance, in patients with Parkinson's disease, increased iron levels within the SN/VTA block DA production (Zecca et al., 2004; Hare and Double, 2016), and cause severe motor impairments. Apart from the SN/VTA, iron in Parkinson's patients also reaches higher levels within the putamen and prefrontal cortex (PFC) compared to healthy controls. Moreover, within the group of Parkinson's patients, brain iron was negatively correlated with cognitive performance (Thomas et al., 2020). In Alzheimer's disease, iron accumulation of frontal cortical areas was positively correlated with the amount of amyloid-ß plaques and tau (van Duijn et al., 2017). Further, a dysfunction of iron metabolism was revealed within the autoimmune disease multiple sclerosis. Within the course of the disease, damaged oligodendrocytes liberate iron within extracellular space, which causes increased iron uptake from microglia and macrophages, and promotes the degeneration of these cells (Hametner et al., 2013; Stephenson et al., 2014).

Importantly, an increase of iron levels within the brain has also been described in healthy aging. It was suggested that the underlying mechanism is an age-related dysfunction of processes that involve iron metabolism, possibly caused by oxidative stress and disturbances within myelin or DA synthesis. In healthy adults, age-related increases in iron levels were found mostly within subcortical structures (Hallgren and Sourander, 1958; Bilgic et al., 2012; Daugherty and Raz, 2013), and the BG (Callaghan et al., 2014; Steiger et al., 2016). Within the striatum, age-related iron accumulation negatively correlated with verbal memory performances (Steiger et al., 2016), suggesting a distortion of dopaminergic neuromodulation, and thus, impaired encoding of novel memory contents.

1.2.4 Dopamine

Midbrain dopaminergic neurons within the SN/VTA release DA which innervates the BG via the nigrostriatal pathway, and the PFC via the mesocortical pathway (Aosaki et al., 1994; Tritsch and Sabatini, 2012; Bissonette and Roesch, 2016). The neurotransmitter DA regulates different

functions of cognition and behavior, such as learning and memory (Puig et al., 2014; Kempadoo et al., 2016), working memory (Landau et al., 2009), executive function (Floresco and Magyar, 2006), motivation (Morita et al., 2013), attention (Li et al., 2006), reward (Pessiglione et al., 2006), novelty processing (Lisman and Grace, 2005), and motor performance (Gepshtein et al., 2014). Moreover, DA has been found to promote plasticity within the striatum where it supports growing of dendritic spines (Yagishita et al., 2014).

A disturbance of the dopaminergic system is related to several psychiatric and neurological processes, such as mood disorders (Ashok et al., 2017; Radwan et al., 2019), addiction (Volkow et al., 2007), attention deficit hyperactivity disorder (Wu et al., 2012), or schizophrenia (Seeman and Kapur, 2000). In Parkinson's disease, decreased levels of DA were revealed within the striatum (Broussolle et al., 1999) and the SN/VTA (Gröger et al., 2014), and are further linked to motor dysfunctions (e.g., bradykinesia, rest-tremor, rigidity; Magrinelli et al., 2016) and non-motor symptoms (e.g., sleep disorders, depression; Chaudhuri and Schapira, 2009).

Besides pathological changes, a loss of DA receptors as well as reduced DA transport are also associated with healthy aging (Kaasinen et al., 2000; Volkow et al., 2000). These age-related changes in the dopaminergic system were linked to impaired cognitive flexibility (Berry et al., 2016), changes in reward processing (Dreher et al., 2008), novelty processing (Bunzeck et al., 2007), and memory impairments (Bäckman et al., 2009; Rieckmann et al., 2018). On the other side, the intake of DA precursor improved recollection in older adults (Chowdhury et al., 2012), which further emphasizes the relevance and sensitivity of dopaminergic modulation on memory performance in aging.

1.3 Reserve, maintenance, and compensation

During healthy aging, cognitive and structural changes can lead to malperformance of many cognitive domains. Nonetheless, huge inter-individual differences in cognitive performance across the life-span have been described (Wilson et al., 2002), which are even more pronounced with increasing age (de Frias et al., 2007). The extent to which brain functions are maintained in late life, might relate to differences in lifestyle and genetic risk factors of the individual

(Nyberg et al., 2012). In the following, three interacting concepts of brain health in higher age will be introduced: reserve, maintenance, and compensation (Cabeza et al., 2018).

Originally, the concept of reserve distinguishes between brain reserve and cognitive reserve. Brain reserve, on the one side, is described as the individual difference in brain structure which allows improved resilience towards brain pathology. Cognitive reserve, on the other side, stands for improved individual task processing that enables enhanced coping with existing brain pathologies (Stern, 2009). However, since cognitive performance cannot be disentangled from the constitution of brain structure (Cabeza et al., 2018), the terms brain reserve and cognitive reserve will be combined in the following. The reserve notion postulates that during childhood and adulthood, the individual aggregates a cumulative reserve via different mechanisms which can compensate or decelerate cognitive decline in late life. Apart from several genetic and environmental factors which might contribute to higher reserve, the educational level of the individual has been the most discussed mechanism (Piras et al., 2011; Meng and D'Arcy, 2012). For instance, it was shown that the years of education correlate with structural integrity within the bilateral hippocampus (Piras et al., 2011). Hence, a given threshold must be reached before a pathology will affect behavior. In line with the reserve notion, a study performing necropsy on 209 individuals reported that 33% of the non-demented individuals showed full pathologic criteria for Alzheimer's disease at post mortem examination (Neuropathology Group. Medical Research Council Cognitive Function and Aging Study, 2001). In other words, despite pathological brain alterations, some individuals seem to be free of behavioral symptoms. This assumption is further supported by several findings reporting that high education can protect against the onset of dementia (Caamaño-Isorna et al., 2006; EClipSE Collaborative Members et al., 2010; Meng and D'Arcy, 2012) and even lower the risk of dementia after suffering a stroke (Mirza et al., 2016). However, another study revealed that the association between higher educational level (beyond 9 years) and cognitive decline is mediated by higher income, which possibly influences cognitive health through several different aspects (Zahodne et al., 2015). Nonetheless, a correlation which was not mediated by income was detected for the lower educational group (up to 8 years). Therefore, the authors suggested a sensitive early developmental phase in which the acquirement of basic

skills might be crucial for later cognitive health. Although the underlying mechanisms between high educational level and protective mechanisms of cognitive decline in late adulthood remain unclear, several factors (e.g., high-quality health care, health-conscious lifestyle, stimulating leisure activities) which might be influenced by higher income, may contribute to the findings (Zahodne et al., 2015).

Another mechanism being linked with the reserve notion, is brain maintenance (Nyberg et al., 2012; Cabeza et al., 2018). While reserve describes the aggregation of protective mechanisms throughout the life-span, maintenance describes how the structure of the brain, which relates to cognitive performance, can be kept constant or repaired (Cabeza et al., 2018). For instance, an individual might have a relatively large hippocampus and thus be more protected against a yearly hippocampal decline. Repair on the other side, describes the improvement (structurally or functionally) of an already altered brain structure (e.g., after a concussion; Russo et al., 2018). In older aged brains however, maintenance becomes more critical and repair cannot fully cover neural damage (Cabeza et al., 2018). While the childhood and early adulthood have been shown to be very sensitive for building a reserve (e.g., through education), some evidence suggests that even in older age, a modulation of specific lifestyle factors can improve maintenance and protect against cognitive decline. For instance, the quality of sleep of older adults can facilitate the onset of dementia, often years before the first symptoms of disease emerge (Lim et al., 2013; Sterniczuk et al., 2013). In a review, Musiek and Holtzman (2016) discussed several mechanisms which can be affected by the lack of sleep, such as inflammatory processes and oxidative stress. Besides sleep, physical exercise has been shown to influence cognitive performance (Erickson et al., 2011; Cheng, 2016; Wikee and Martella, 2018). Specifically, aerobic exercises can lead to a reduction of GM volume loss (Boraxbekk et al., 2016), decrease the risk of vascular diseases (Mobasseri et al., 2015), promote plasticity (Kempermann et al., 2010), and lower the risk of developing dementia (Luck et al., 2014). Moreover, it was shown that cognitive training could improve WM integrity (Engvig et al., 2012), and increase cortical thickness (Engvig et al., 2010) in older adults. Noteworthy, older adults that maintain episodic memory abilities as they age show less hippocampal volume loss compared to those, which show decline during a 4-year period (Gorbach et al., 2017). Hence,

there are reasonable grounds that even in higher age, lifestyle factors can be targeted and manipulated to enhance maintenance by stabilizing or improving brain structure and cognition.

In contrast to reserve and maintenance, compensation is described as a mechanism of neural recruitment. Within high cognitive demands, neural resources are recruited from usually unengaged brain networks. The mechanism operates under several conditions, however, in the aging brain, compensation is mostly caused by neural decline (e.g., atrophy) (Cabeza et al., 2018). On the neural basis, functional magnetic resonance imaging (fMRI) findings indicate two forms of age-related compensation: One is described as the compensation-related utilization of neural circuits hypothesis (CRUNCH; Reuter-Lorenz and Cappell, 2008), and explains overactivation often found in older compared to younger adults. The other form of compensation, called hemispheric asymmetry reduction in older adults (HAROLD; Cabeza, 2002), describes a reduced lateralization in the PFC. Both forms outline the recruitment of neural resources by means of a functional shift to additional brain networks to compensate age-related brain alterations, and to improve cognitive performance (Cabeza et al., 2018). Cabeza et al. suggested that first an impairment of a task related structure must occur before an additional brain network compensates for this malfunction. Importantly, the authors concluded that a network shift must result in improved performance, because elsewise, without the direct link to performance, differences between younger and older adults cannot account to a compensation mechanism. Previous studies could already demonstrate an age-related over-activation of the dorsolateral PFC at lower working memory loads, while in younger participants, the same areas were activated only within higher loads. Importantly, differences in performance at lower working memory loads between both age groups were marginal, further providing evidence for age-related compensation (Cappell et al., 2010).

In summary, healthy aging depends on several different factors and interplaying mechanisms. First, there is a body of evidence showing that an individual can accumulate a certain reserve of cognitive functioning during the life-span. Second, in older age, the maintenance of brain functions becomes more and more important. Active repair processes but also inter-individual variations in different properties (e.g., volume of hippocampus)

contribute to better or worse performance. Third, age-related compensation shifts of brain networks can result in improved performance. The findings suggest that older brains have several strategies to cope with pathology. These can be addressed throughout different interventions, targeting cognitive, environmental or lifestyle factors which can contribute to increased cognitive reserve and activate potential resources in older adults (Reuter-Lorenz and Cappell, 2008).

1.4 Cognitive training

Research emphasizes the importance of late life (micro-)structural reorganization and plasticity (Burke and Barnes, 2006; Li et al., 2008; Smith, 2013; Gutchess, 2014), which enables life-long learning and an adaption to environmental changes. It could be shown that even in higher age, people are able to enhance their performance in many domains, such as learning a foreign language (Klimova, 2018), or improving a certain skill (e.g., juggling; Boyke et al., 2008). Interestingly, second language acquisition in older adults improved global cognition and functional connectivity (Bubbico et al., 2019). Similarly, daily piano lessons in older adults led to increased performance in executive functioning (as tested by the Stroop task) (Seinfeld et al., 2013). Besides cognitive interventions, physical interventions were shown to increase hippocampal volume in older adults, resulting in an improvement of spatial memory abilities (Erickson et al., 2011). These findings suggest that a training induced stimulation of brain regions can also be beneficial for other untrained abilities (so-called transfer effects), which rely on a common network.

During the last decades, cognitive trainings, especially for the older population, have raised the interest of many researchers and several studies revealed promising results. Specific trainings have been applied in different settings, for instance clinical intervention (e.g., Parkinson's disease; Walton et al., 2016), neurofeedback (Angelakis et al., 2007), meditation (Tang and Posner, 2009), exposure to nature (Kaplan, 1995) or physical activity (Erickson et al., 2011). Transfer effects have been explained by functional (e.g., increased DA release; Bäckman et al., 2017) and structural (i.e., increase in cortical thickness; Engvig et al., 2010) changes due to the respective sort of training.

1.4.1 Working memory training

In contrast to long-term memory (LTM), in which information can be stored and recollected over an infinite period of time, working memory capacity is restricted to a small amount of information segments. These segments are memorized only for a short duration and are not further transmitted into LTM formations. Alan Baddeley (Baddeley, 1992) discriminated three famous working memory components: The phonological loop, responsible for rehearsal of phonologic material, the visuospatial sketchpad, which temporarily stores visual stimuli, and the central executive, which controls the attentional system and mediates between the phonological loop and the visuospatial sketchpad. Working memory is processed within several brain regions within the PFC and parietal cortex (Owen et al., 2005), but is also linked to subcortical areas as the BG (McNab and Klingberg, 2008).

With increasing age, working memory performance declines (Salthouse, 1991; West, 1999; Bowles and Salthouse, 2003; Wang et al., 2011), leading to a distraction of attentional cognitive control mechanisms. Using fMRI, age-related working memory impairments correlated with deficits in the suppression of cortical activity, which is linked to the processing of task-irrelevant information (Gazzaley et al., 2005). Notwithstanding, intact working memory performance is crucial for many daily tasks, as it supports attentional processes that suppresses distracting and irrelevant information (West, 1999). Moreover, age-related differences in cognition are mediated by working memory impairments (Salthouse, 1991). Interventions with the aim of maintaining or decelerating working memory capacity loss in older adults are therefore highly in need.

Hence, it is not surprising that working memory training approaches for the older population have been investigated extensively (Li et al., 2008; Richmond et al., 2011; Heinzel et al., 2014, 2016). A frequently used working memory paradigm is the n-back task. Here, subsequent displayed items have to be manipulated (i.e., updated) within a mental representation over short time intervals (Veltman et al., 2003). While there are different kinds of n-back tasks (e.g., dual, visual, auditory), within the visual numeric n-back task, random numbers are presented on a computer screen, separated by a fixation cross. The participants are instructed to press a button every time a number appears that has been shown, for instance,

two items before (i.e., 2-back). On the neural level, the n-back task has been linked to activations within the dorsolateral and the ventrolateral PFC and the parietal cortex. Using this paradigm, it was demonstrated that trainings led to improvements in the trained n-back task (Jaeggi et al., 2008; Heinzel et al., 2016; Salminen et al., 2016), but more importantly, also could improve untrained abilities. Specifically, it was shown that working memory training may enhance Gf (Jaeggi et al., 2008; Heinzel et al., 2016), processing speed (Heinzel et al., 2016), executive function (Heinzel et al., 2016), and verbal memory (Richmond et al., 2011).

In the paradigm from Heinzel et al. (2016), from which we adapted several aspects, a high sensitivity of the n-back task in older adults was demonstrated. More precisely, a 4-week training (45 min 3 times a week; in total 12 sessions) of a n-back task with varying working memory loads (0-, 1-, 2-, and 3-back) adapted to individual level, was tested. Healthy older adults were examined using a cognitive assessment and fMRI scans. Before and after the training period, the participants performed the n-back task within a fMRI scanner, and the blood-oxygen-level-dependent (BOLD) signal was measured. As a result, participants improved in the trained n-back task, and transfer to executive functioning, processing speed, and Gf was reported. Moreover, a decrease in BOLD signal in the training group was revealed within the right lateral middle frontal gyrus/caudal superior frontal sulcus, suggesting increased efficiency in working memory processing.

1.4.2 Pending issues and novel approaches

Despite aforementioned promising results, several studies failed to detect a transfer to untrained abilities and criticize an overestimation of training benefits (Owen et al., 2010; Shipstead et al., 2010; Redick et al., 2013). It has further been stated that cognitive training studies often follow a publication bias in favor of positive outcomes, neglecting small effect sizes and include inadequate control groups (Rabipour and Raz, 2012). However, since both, striatal activity (Dahlin et al., 2008) and DA release within striatal areas (Bäckman et al., 2017) have been reported to increase after working memory training, a positive effect to other domains dependent on striatal integrity seems feasible. Dopaminergic and striatal activity as well as structural integrity have been shown to be of high importance for several cognitive domains (Provost et al., 2015) besides working memory (Landau et al., 2009). This includes

verbal memory (Steiger et al., 2016), associative memory (Puig et al., 2014; Bauer et al., 2015), learning (Foerde and Shohamy, 2011), executive function (Leroi et al., 2013), and Gf (Rhein et al., 2014). Therefore, training related improvements of structural integrity of the BG could positively modify the dopaminergic circuit and therefore, enhance performance in the aforementioned cognitive domains.

Nonetheless, many questions concerning the benefits and neural mechanisms of cognitive training remain unanswered. To further tackle this issue, it has been suggested to intermix cognitive training paradigms with elements that target the dopaminergic system (Buitenweg et al., 2012), which is strongly involved in memory and learning processes (Wise, 2004; Chowdhury et al., 2012). In order to address dopaminergic neuromodulation in the line of cognitive trainings, the positive benefits of novelty exposure (e.g., watching national geographic nature movies in between the training tasks) have been discussed (Buitenweg et al., 2012). Combining cognitive training with novelty exposure may additionally activate the dopaminergic mesolimbic system and therefore, enhance positive training effects.

1.5 Dopaminergic novelty processing

In humans, both, the presentation of novel images and the exposure to a novel virtual reality (VR) before a word-learning phase have been shown to improve subsequent memory performance (Fenker et al., 2008; Schomaker et al., 2014). Interestingly, studies in animals found that memory was not only improved by novelty exposure before, but also after the initial learning phase (Wang et al., 2010a).

The underlying mechanisms of novelty processing have been described by the hippocampal-VTA loop model by Lisman and Grace (2005). The authors explain how novel stimuli can enhance long-term potentiation (LTP) and facilitate learning processes. When a novel stimulus is detected by the hippocampus, the hippocampus and surrounding parahippocampus compare the novel information with memory content that is already stored within the LTM. Once the information has been classified as novel, the hippocampus sends a novelty signal over the subiculum towards the NAcc. The PFC sends a signal to the NAcc when the information is not only novel but also goal directed and important for motivational future behavior. The combination of novel and goal directed signals within the NAcc regulates the

filtering of novel but irrelevant information. Subsequently, the novelty signal is transmitted via the ventral pallidum to the VTA. Here, the pedunculopontine receives inputs of stimulus salience from the limbic system and the PFC. The information regarding goal-direction and salience controls firing of the dopaminergic cells within the VTA, which are sent via an upward loop back to the hippocampus where DA is released. Finally, DA within the hippocampus enhances LTP, which in turn promotes synaptic plasticity and learning (Lynch, 2004; Kumar, 2011; Bromer et al., 2018), and thus, enables storage of relevant novel information within the LTM (**Figure 1.1**; Lisman and Grace, 2005).

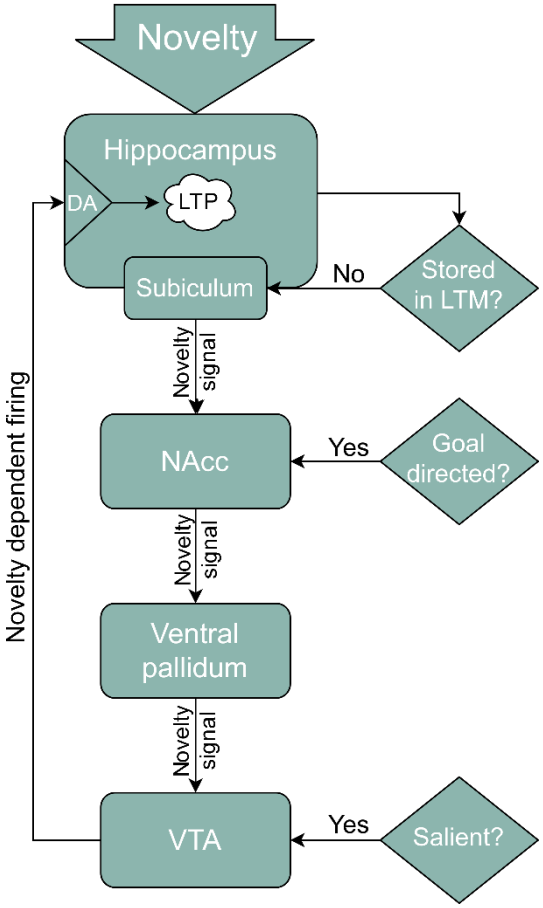

Figure 1.1. Simplified schematic description of the hippocampal-VTA loop (adapted from Lisman and Grace, 2005). When the hippocampus detects a novel information, a signal is send via the subiculum and the nucleus accumbens (NAcc) to the ventral pallidum and finally reaches the ventral tegmental area (VTA). When the novel information is goal directed and salient, dopaminergic cells are activated within the VTA, and via a backward loop sent to the hippocampus, were dopamine (DA) is released and long-term potentiation (LTP) enhanced.

Along the same lines, animal studies demonstrated that exposure to spatial novelty could promote DA-dependent LTP within the hippocampus. Specifically, it was shown that when

D1/D5 receptors were blocked, no LTP could be induced. The reverse effect was observed when these receptors were activated in anesthetized animals and LTP promotion facilitated (Li et al., 2003). In humans, evidence for the hippocampal-VTA loop model comes from fMRI findings, which detected a novelty-driven activation within the SN/VTA (Bunzeck and Düzel, 2006). It was further revealed that the exposure to novel images (Fenker et al., 2008), a novel VR (Schomaker et al., 2014) or a novel science lesson in school children improved subsequent memory performance (Ballarini et al., 2013).

In the consequences of age-related changes in DA (Bäckman et al., 2006), processing of novel stimuli can be disturbed. Supporting the notion of a hippocampal-VTA loop model (Lisman and Grace, 2005), it was shown that in older adults the hemodynamic response to novel stimuli correlated positively with structural integrity of the SN/VTA and the hippocampus (Bunzeck et al., 2007). However, despite reduced responses to novel stimuli compared to young adults, older aged people may benefit from the positive effects of novelty exposure. For instance, complex leisure time activities are supposed to improve intellectual performance (Schooler and Mulatu, 2001), and several studies emphasize the positive effects of a stimulating environment on mental and cognitive processes in older age (Hultsch et al., 1999; Lövdén et al., 2005; Small et al., 2012; Leon and Woo, 2018). Hence, exposure to novelty may have attenuating effects on age-related cognitive decline and therefore, may contribute to promote plasticity in older aged brains.

1.6 Research aim

Previous studies revealed behavioral and structural age-related alterations that are not restricted to pathology, but also occur during healthy aging. Importantly, inter-individual differences and lifestyle factors which contribute to cognitive reserve have been discussed, suggesting an active participation in the process of healthy aging. Cognitive trainings have been linked to brain plasticity and the possibility to improve untrained cognitive abilities which are not related to the trained task. However, recent doubts concerning the effectiveness of cognitive training programs have arisen and studies failed to replicate positive findings (Owen et al., 2010; Shipstead et al., 2010; Redick et al., 2013). A possible approach to improve training gains introduced by Buitenweg et al. (2012) is to include novelty in the paradigm. The

underlying rationale is that exposure to novelty stimulates the mesolimbic dopaminergic system (Lisman and Grace, 2005), which in turn is involved in working memory processes (Dahlin et al., 2008; McNab and Klingberg, 2008; Bäckman et al., 2017).

On this basis, the thesis' objectives evolve as follows: To investigate a) microstructural processes of healthy aging and their link to cognition, b) the underlying neural mechanisms of cognitive training by combining an established working memory training with exposure to novelty, and c) whether a passive exposure to novelty improves subsequent memory performance. To that end, behavioral and diagnostic measurements as well as neuroimaging by means of structural MRI were performed.

In study 1, the baseline data of the cognitive training study were analyzed. Here, GM volume, myelin, and iron marker within the BG were correlated with age and cognitive performance. We expected age-related decline in GM and myelin and an increase of iron levels. Moreover, we hypothesized that GM volume and myelin correlate positively, and iron negatively with cognitive performance.

In study 2, the effects of the 4-week working memory training (i.e., 2-back), which was combined with the exposure to novelty in healthy older adults were examined. The rationale was that novelty has been shown to activate the mesolimbic dopaminergic system and to improve subsequent memory performance. Therefore, we hypothesized that novelty enhances training gains and transfer effects.

In study 3, an additional experiment was performed testing the effects of novelty exposure on subsequent memory performance in a young cohort. Based on the previous literature, we assessed exposure to novelty at three different time points (15 min before, directly after, and 15 min after an encoding task), and expected that novelty improves subsequent memory performance.

In the following, the applied general methods and the manuscripts of the three studies are presented. Finally, in the general discussion, findings will be summarized and integrated. Moreover, challenges of intervention models, limitations, and future directions will be reviewed. **Figure 1.2** depicts an overview of the research objectives of the present thesis.

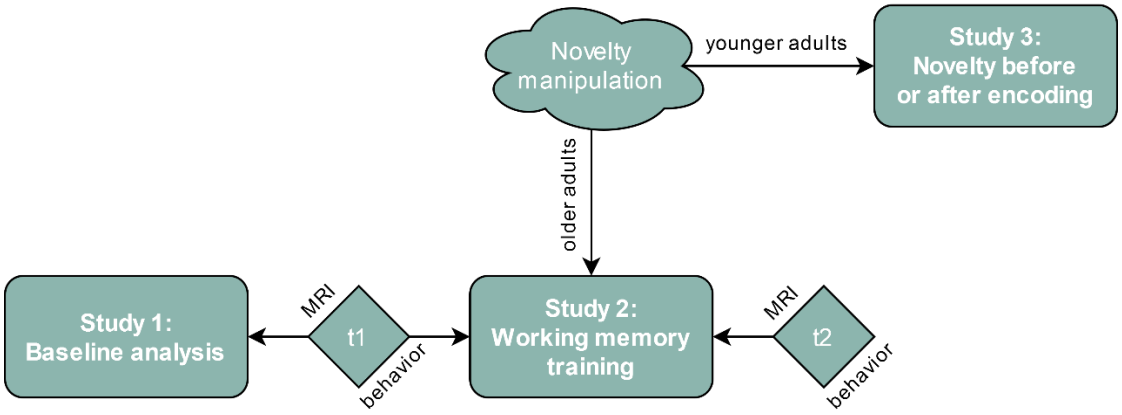

Figure 1.2. Integration of research objectives. A 4-week working memory training intermixed with novel nature movie sequences in healthy older adults was performed. Data (structural MRI and behavior) were acquired at two time points (t1 and t2). In study 1, behavioral performance was correlated with structural integrity (t1 data only). In study 2, effects of the cognitive training were analyzed (t1 and t2). In study 3, it was investigated whether novelty improves subsequent memory performance in a younger cohort.

General methods

- Structural magnetic resonance imaging
- Multiparameter mapping
- Voxel-based morphometry and voxel-based quantification

2 Structural magnetic resonance imaging

Since its first application in the 1970s (Lauterbur, 1973), MR imaging became indispensable for the medical anamneses of brain and body. Continued efforts for improving MR contrasts and novel analysis tools resulted in increased sensitivity of different tissue classes. In the present thesis, structural MRI was used since we were mainly interested in subcortical differences of GM volume, myelin, and iron levels. Specifically, it was investigated how structural integrity relates to cognitive performance (study 1), and whether microstructure can be positively modulated by a cognitive training intervention (study 2). In the next sections, a brief overview of the principal MRI functionality and main components will be given, followed by an introduction of the applied multiparameter mapping (MPM) approach, and the imaging analyses using voxel-based morphometry (VBM) and voxel-based quantification (VBQ).

2.1 Principal MRI functionality

An MRI acquisition is determined by the interplay of three interacting components: the static magnetic field (B0), the radio frequency (RF) coils, and the gradients. The central biological element which is measured by an MRI scanner are the nuclei of hydrogen atoms, the positively charged protons, which have an intrinsic angular momentum (i.e., a spin). When a strong magnetic field is applied, the proton is repositioned parallel or antiparallel (longitudinal magnetization) to the magnetic field of the MR scanner (B0), which represents the z-axis. The Larmor ($\omega 0$) frequency describes the precession movement of the spin and can be calculated using the following formula: $\omega 0 = \gamma 0 \times B0$, while $\gamma 0$ is a constant in MHz (for a proton 42.58 MHz) and B0 the applied magnetic field in Tesla (e.g., 3). In addition, a RF impulse, which is equal to the Larmor frequency, can be applied to the B0 field (resonance condition). As a result, the spins are excited, and dependent on the applied pulse, different alignments (e.g., 90°) of the spins can be induced. On this way, the spins can be redirected from the z-axis (B0) to the x/y-axis. Moreover, an additional magnetic coil is installed, which enhances the magnetic field at the head of the scanner and weakens the magnetic field at the foot end of the scanner. Thereby, the magnetic field becomes inhomogeneous, which enables to stimulate each slice separately by their own Lamour frequencies. The slice thickness is determined by the strengths of the gradient, while a stronger gradient results in thinner slices and a weaker gradient in

thicker slices (Weishaupt et al., 2014). Finally, by use of sensitive MR computer, the MR signal for each slice can be processed and combined into a 3D image.

2.2 Imaging contrasts

The longitudinal relaxation (T1) describes a time constant in which the excited protons tilt back to B0. In addition to T1, the transversal relaxation (T2 or T2*) can be measured. When a RF pulse is applied, all spins are in phase (i.e., all directed to 0°), but with time, the spins dephase and lose their coherence. This induces that the magnetic vectors start to cancel each other out, resulting in a loss of the MR signal (i.e., T2). T2* describes an additional dephasing due to inhomogeneities of B0. Therefore, the dephasing of T2* is faster compared to T2. These inhomogeneities can be induced by tissue boundaries or iron particles, which lead to local magnetic fields. Apart from T1, T2, and T2*, the proton density (PD) can be calculated. PD reflects the maximal signal of spins within a tissue. Depending on which MR weighting has been applied, different tissue properties become visible (Weishaupt et al., 2014).

Moreover, several MR parameters (e.g., TR = repetition time; TE = echo time; flip angle) can be adjusted to obtain the preferred MR image contrast. TR is the duration between two RFs, and determines, together with the longitudinal relaxation time (i.e., T1) the image contrast. When a short TR is applied, tissue types with a short T1 relax fast, resulting in a lighter image contrast. On the other hand, in tissue types with a long T1, a short TR does not give the spins enough time to relax before they are excited again, resulting in a reduced signal and a darker contrast. A long TR results in a reduction of T1 weighting since all tissue types (with a short as well as a long T1) have enough time to relax and show a similar MR signal (Weishaupt et al., 2014).

Another adjustable MR parameter is the TE. The TE represents the duration between impulse and MR signal recording. Using a short TE, the influence on the T2 images is not very high, due to low signal intensity differences. In a long TE, signal intensity differences are stronger, which is observable in higher image contrasts. In a short T2 most signal intensities are lost already before recording, which produces darker contrasts, while a long T2 results in brighter images (Weishaupt et al., 2014).

Finally, the flip angle represents a usable adjustable parameter to overcome time related obstacles. Using a short TR, not all spins have enough time for a longitudinal relaxation to B0, which ends in signal loss. A way to overcome this issue in fast MR sequences, is to reduce the flip angle. In other words, instead of relocating the spins to 90°, the angle can be adapted (for instance) to only 30° (Weishaupt et al., 2014).

In sum, structural MRI contrasts can be modulated by adaptions of TR, TE, and flip angles, and hence provide sensitive information of different tissue classes.

2.3 Multiparameter mapping

In the present study, MPM, which provides the main contrast images within a single MR acquisition was applied. The high resolution of the images allows a distinct discrimination between microstructural properties, hence, MPM has been used in clinical studies (Seif et al., 2018) but also healthy aging research (Draganski et al., 2011; Callaghan et al., 2014; Steiger et al., 2016). For the present study, we applied a processing pipeline of 1 mm isotropic resolution for weightings of T1, magnetization transfer (MT), and PD, within a 20 min acquisition time. The weightings were obtained by different TRs, TEs, and flip angles (Weiskopf and Helms, 2008; Weiskopf et al., 2013), and were further processed to obtain quantitative maps of MT and the effective transverse relaxation rate (R2*).

MT is described as the magnetization exchange between mobile protons within free fluid and less mobile protons which are bound in macromolecules. The excitation of macromolecular protons by an RF pulse leads to a subsequent saturation of magnetization, which spreads to the surrounding mobile protons. The resulting signal loss depends on the relation between macromolecules and free fluid, and provides information of tissue composition (Graham and Henkelman, 1997; Henkelman et al., 2001; Weishaupt et al., 2014). Bound protons are found in myelin, therefore, MT saturations have been strongly linked to myelination (Filippi and Rocca, 2007; Hagiwara et al., 2018; Sled, 2018), as post mortem studies could confirm (Schmierer et al., 2004). Due to its myelin sensitivity, MT is often assessed within pathologies affecting the myelin system along WM pathways. Within the autoimmune disease multiple sclerosis, WM structures are strongly affected by demyelinating processes, and reductions of WM MT have been reported extensively (Mehta et al., 1996; Filippi et al., 1999;

Chou et al., 2018). Importantly, also within GM structures (e.g., BG) a decline of MT ratio (MTR) was linked to early multiple sclerosis (Audoin et al., 2004; Khaleeli et al., 2008). Moreover, decreases in GM MTR of the whole brain and the hippocampus have been linked to Alzheimer's disease (Bozzali et al., 2001; Ridha et al., 2007), but also in healthy aging, a decrease of MT has been observed within GM and WM structures (Callaghan et al., 2014; Seiler et al., 2014).

Besides its sensitivity to myelin, MT maps have been shown to provide a good contrast between structures and hence, are well suited for VBM or VBQ segmentation of different tissue classes (Helms et al., 2009; Lorio et al., 2014).

R2* (=1/T2*) is a relaxation parameter which is strongly linked to iron, since paramagnetic metals within the tissue lead to a faster decrease of the MR signal of a gradient echo sequence (Langkammer et al., 2010; Callaghan et al., 2015). Therefore, R2* as an indicator of iron is frequently used within liver (Wood et al., 2005; Storey et al., 2007) or heart (Storey et al., 2007; Wang et al., 2010b) iron assessment, but also finds its application in the estimation of non-heme brain iron (Langkammer et al., 2010). While iron accumulations within brain tissue are strongly linked to pathology (e.g., van Duijn et al., 2017; Thomas et al., 2020), they are also a hallmark of healthy aging (Callaghan et al., 2014; Steiger et al., 2016).

In sum, MT and R2* maps are well-established in vivo imaging parameters for the detection of age-related tissue changes of myelin and iron within subcortical structures. Particularly within the BG, both parameters show sensitivity to microstructural changes and are therefore well suited for the present research questions (Callaghan et al., 2014; Steiger et al., 2016).

2.4 Voxel-based morphometry and voxel-based quantification

VBM and VBQ enable voxel-wise analysis of brain tissue between groups, by normalizing the brains to their own specific group template (Ashburner and Friston, 2000). Both analysis techniques were applied using the Statistical Parametric Mapping (SPM 12, Wellcome Trust Center for Neuroimaging, London) package within MATLAB (R2014b version, Mathworks) software.

In the present thesis, VBM was used for the analysis of GM, since the method provides a good discrimination between GM, WM, and CSF (cerebrospinal fluid), and therefore, a reliable

estimation of GM volume. In a first preprocessing step, the tissue is segmented into GM, WM, CSF, and three other tissue classes using the individual MT maps. To provide an adequate segmentation and to avoid partial volume effects, a high image resolution (1 or 1.5 mm^3) is recommended (Ashburner and Friston, 2000). In a next step, the diffeomorphic registration algorithm (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra; DARTEL) is applied. DARTEL improves the accuracy of inter-subject alignment by generating a group specific template on which the individual images are registered to (Ashburner, 2007). Within the normalization process, the template generated in DARTEL is registered to Montreal Neurological Institute (MNI) space, so that the individualized scans are also adapted to MNI space. Within VBM, the images are further modulated (Jacobian scaled) and smoothed using a Gaussian kernel of 6 mm full width at half maximum (FWHM), which ensures that the amount of tissue is preserved. Specifically, each voxel within the smoothed image represents the average concentration of GM tissue (range 0-1) for the surrounding voxel (Ashburner and Friston, 2000).

For the analysis of myelin (i.e., MT) and iron (i.e., R2*) marker, VBQ, which is well suited for the detection of subcortical tissue changes, was applied. Here, we followed the automated hMRI processing pipeline (Tabelow et al., 2019). While the processing steps of segmentation and DARTEL are identical to the VBM approach, differences are present within the normalization of images. In detail, within VBQ, images are not modulated (i.e., no Jacobian scaling), to preserve the concentration of different tissue types. In order to enhance tissue specificity, a tissue-weighted Gaussian smoothing of 3 mm at FWHM back in native space is applied. Using this approach, parameter volume changes which occur using Gaussian smoothing in standardized space, can be avoided (Draganski et al., 2011).

After image processing of VBM and VBQ, general linear model (GLM) statistics on the resulted statistical parameter maps can be applied within the SPM package to investigate differences between groups (Ashburner and Friston, 2000). **Figure 2.1** provides an overview of the image processing pipeline.

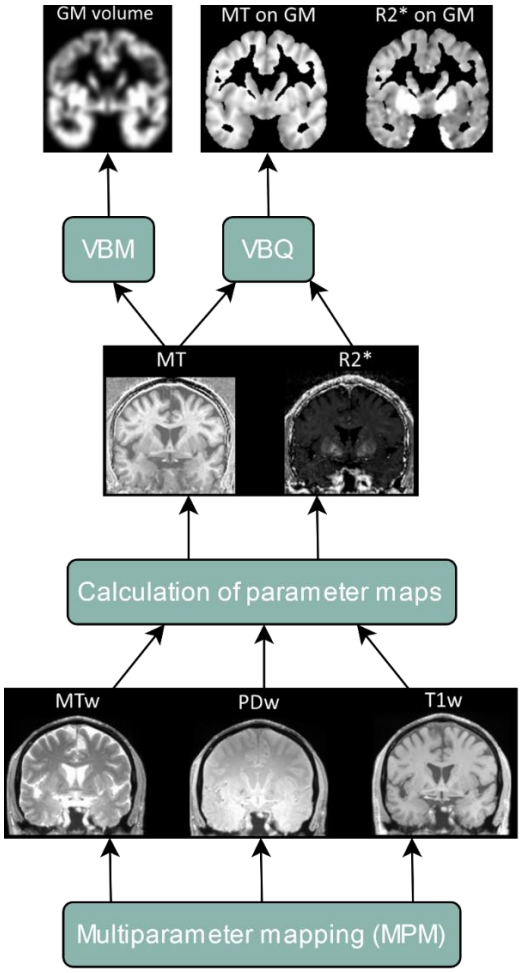

Figure 2.1. Analysis pipeline of structural MRI data of one participant. In a first step, multiparameter mapping (MPM) following Weiskopf and Helms (2008) and Weiskopf et al. (2013) was applied to obtain images of different weightings (magnetization transfer [MTw], proton density [PDw], and T1w). Subsequently, parameter maps (MT and R2*) were processed (Helms et al., 2008a, 2008b; Helms and Dechent, 2009). For the VBM and VBQ analysis, MT maps were used for segmentation. For the VBM analysis, the MT maps were normalized, modulated, and smoothed (Ashburner, 2015). For the VBQ analysis, MT and R2* parameter maps were normalized, underwent a tissue-weighted smoothing (Draganski et al., 2011), and were calculated for GM subspace (Tabelow et al., 2019).

Manuscripts

- Age-related iron accumulation and demyelination in the basal ganglia predict verbal memory and executive functioning

- The gains of a 4-week cognitive training are not modulated by novelty

- Novelty before or after word learning does not affect subsequent memory performance

3 Study 1: Age-related iron accumulation and demyelination in the basal ganglia predict verbal memory and executive functioning

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Abstract

Age-related cognitive decline has been linked to alterations of the dopaminergic system and its subcortical trajectories. Recent work suggests a critical role of iron accumulation within the BG in verbal memory performance, and increased iron levels have been related to demyelination. However, the specificity of age-related iron increases with respect to cognitive functions remains unclear. Therefore, we investigated the interplay of age, cognitive performance, and structural integrity of the BG. In total, 79 healthy older participants underwent a broad cognitive assessment (fluid and crystallized intelligence, verbal and numeric memory, processing speed, executive functions) and structural MRI. As expected, performance in most cognitive tests had a negative relationship with age. Moreover, BG grey matter volume and MT (indicative of myelin) decreased, and R2* (indicative of iron) increased with age. Importantly, R2* and demyelination negatively correlated with verbal memory and executive functions. Within the SN/VTA age correlated negatively with MT, but there was no clear evidence in favor of a relationship between behavior and R2* or MT. Our results suggest that age-related increases in iron and demyelination within the BG, which are part of a fronto-striatal network, not only impact on verbal memory but also executive functions.

3.1 Introduction

Cognitive declines in healthy aging have previously been linked to cortical and subcortical degeneration (e.g., Hedden and Gabrieli, 2004), but the underlying microstructural changes are poorly understood. In this regard, recent studies could show that iron accumulations within the BG closely relate to demyelination and deficits in verbal LTM performance (Daugherty et al., 2015; Steiger et al., 2016). The specificity of BG iron accumulations on cognitive functioning, however, remains unclear.

In contrast to GM and myelin, iron is mainly located in subcortical structures (Hallgren and Sourander, 1958; Bilgic et al., 2012; Daugherty and Raz, 2013). Within the BG and interconnected SN/VTA, increased iron levels are typically related to motor problems in neuropsychiatric diseases (i.e., Parkinson's disease; Sian-Hülsmann et al., 2011; Hare and Double, 2016), but they are also a hallmark of healthy aging (Raz et al., 2005). Importantly, iron accumulations have been further related to demyelination (Haider, 2015; Lassmann and van Horssen, 2016), and a recent study observed a negative association between iron levels and myelination within the striatum (Steiger et al., 2016).

At the cellular level, glia cells (i.e., oligodendrocytes) require iron for myelin production (Todorich et al., 2009), but as iron accumulates, oxidative stress can damage the myelin sheaths (Connor, 2004). Besides its role in myelin production, the non-heme iron enzyme tyrosine hydroxylase is an important factor for the synthesis of DA (Zecca et al., 2004). However, elevated iron levels within the SN/VTA block DA production and even promote cell death (Zecca et al., 2004; Hare and Double, 2016). Indeed, in Parkinson's disease, which is characterized by increased iron levels (Wang et al., 2016), DA transport is reduced within the SN/VTA (Kastner et al., 1993; Toulorge et al., 2016) and further accompanied by a volume loss (Kashihara et al., 2011). In healthy older adults, SN/VTA iron levels do not appear to be increased (Zecca et al., 2001; Li et al., 2015), but the structural integrity of the SN/VTA, as measured with MTR (a marker of myelination; Schmierer et al., 2004) was reduced and predictive of verbal memory performance (Düzel et al., 2008). However, the relationship of iron and myelin within the SN/VTA in healthy aging remains little understood.

Within the brain, iron can be observed in two different forms: heme iron and non-heme iron. While heme iron is functionally linked to the hemoglobin molecule, and therefore exclusive within circulating or accumulating blood; non-heme iron is present within virtually all brain cells (Hallgren and Sourander, 1958; Hametner et al., 2013) and involved in numerous metabolic functions (Daugherty and Raz, 2015). Importantly, MRI based structural measures of iron, such as R2* that we employed here, are supposed to reflect non-heme iron. For a more detailed review see e.g., Daugherty and Raz (2015).

Apart from age-related iron accumulations, decreases in GM volume (Brickman et al., 2007) and myelin (Peters, 2002; Callaghan et al., 2014) have been reported. GM volume loss is typical throughout the cortex, including frontal brain regions (Draganski et al., 2011; Callaghan et al., 2014), but it can also be observed within the hippocampus (Raz et al., 2004), putamen (Callaghan et al., 2014), and caudate (Raz et al., 2005; Bauer et al., 2015). Age-related demyelination, on the other hand, has been found within WM structures, including frontal and parietal regions, the optic radiations, the corpus callosum, and the corticospinal tract (Draganski et al., 2011; Callaghan et al., 2014). A decrease of myelin within GM has been described within the thalamus, Heschl's gyri, the caudate nucleus, and the cerebellum (Callaghan et al., 2014).

Here, we conducted a detailed cognitive assessment (i.e., fluid and crystallized intelligence, verbal memory, numeric memory, processing speed, and executive functions) to further investigate the link between cognitive performance and in vivo structural integrity of the BG in healthy older adults. We performed VBM to quantify GM volume, and VBQ to examine MT and R2*. Both markers, MT and R2*, strongly correlate with myelin and iron concentrations, respectively, as revealed by post mortem studies (Schmierer et al., 2004; Langkammer et al., 2010). With regard to age, we had three major hypotheses: (a) GM volume decreases (Brickman et al., 2007), (b) MT decreases (Peters, 2002), and (c) R2* increases (Callaghan et al., 2014) relative to the tested age range. Additionally, we expected that (d) R2* negatively correlates with MT within the BG (Peters, 2002; Steiger et al., 2016), and we hypothesized that structural integrity (a-c) correlates with cognitive performance. Finally, a voxel-based region of interest (ROI) analysis was conducted for the SN/VTA to explore the relationship between MT, R2* levels and cognitive performance.

3.2 Materials and methods

3.2.1 Experimental design, procedure, and participants

All participants were part of a cognitive training study, which included a test at baseline (t1), a four-week cognitive training, and a follow up examination (t2) at the University of Lübeck. At both time points, all participants received a detailed neuropsychological assessment (see below) and a structural MRI scan (see below). For the current study, only baseline data (t1) were analyzed. The findings of the cognitive training study are reported elsewhere (Biel et al., 2020). Note that the methods sections of cognitive assessment, image acquisition, and VBM/VBQ processing are adapted from Biel et al. (2020).

In total, 92 healthy, right-handed, German speaking older adults were recruited. However, nine participants were excluded due to a history of neurological, psychological or other severe physical disorders, drug abuse, CNS affecting medication intake (less than 2 weeks before testing), non-removable metal implants or claustrophobia. Four additional participants had to be excluded due to technical issues or structural abnormalities observed in the MRI data. Moreover, participants were excluded with > 5 points in the Geriatric Depression Scale (GDS, max. 15 points, > 5 points indicates mild depression; Sheikh et al., 1991) and < 22 points in the Montreal Cognitive Assessment (MoCA, max. 30 points; Nasreddine et al., 2005; Freitas et al., 2013). A value of 22 was chosen based on a study by Freitas et al. (2013), suggesting that it might be an appropriate cut-off for mild cognitive impairment (MCI). Finally, 79 participants (age range 50-80 years, mean age 63.54 ± 8.48, 39 females) completed the MRI sessions and could, therefore, be included in further analyses. Within this group, the following numbers of participants per cohort were included: 50-60 years n = 32, 61-70 years n = 28, 71-80 years n = 19.

Participants were recruited through announcements in the local newspaper or the database of the University of Lübeck (Greiner, 2015). All participants signed a written informed consent and received monetary compensation. The study was approved by the local ethical committee of the University of Lübeck, Germany, and in accordance with the Declaration of Helsinki.

3.2.2 Cognitive assessment

Neuropsychological tests tapped into Gf and Gc, verbal and numeric memory, processing speed, and executive functions. Gf was measured by the German Leistungsprüfsystem (LPS 50+) short version (for people aged 50-90 years; Sturm et al., 2015), which includes a battery of time restricted paper pencil tasks (duration ~30 minutes). For Gc, the German Mehrfachwahl-Wortschatz-Test (MWT; Lehrl et al., 1991; Lehrl, 1995) was applied; it provides 37 rows, each containing four pseudo-words and one correct word, which has to be identified (with no time restriction).

Verbal memory was examined using the verbal learning memory test (VLMT; Helmstaedter et al., 2001). Here, a word list of 15 nonrelated items was verbally presented for five subsequent times. Each time, participants were asked to recall as many words as possible. Recalled words were noted from the examiner (total sum of correctly recalled words of all five runs refers to VLMT learning in further analysis). In a sixth run, an interference list of 15 words was verbally presented, which had to be immediately recalled. Subsequently, participants were asked to recall words from the initial list (without further verbal presentation from the examiner). After 20 min (again without further verbal presentation), the initial word list had to be recalled (VLMT free recall). Consolidation loss (VLMT cons) is calculated by subtracting the amount of words remembered in the fifth round from VLMT free recall. Finally, a recognition task was conducted by presenting the initial word list intermixed with words from the interference list and previously not presented new words. The list was read out aloud and participants had to judge whether they recognized a word from the initial word list or not (VLMT recognition).

Numeric short-term memory was assessed by using a digit span forward and backward test (forward: starting with 3 digits, ending with 8 digits or after 2 errors within the same difficulty level; backward: starting with 2, ending with 7 digits or after 2 errors within the same difficulty level; Wechsler, 1987). Subsequently, scores of digit span forward and backward were summed up.

Processing speed and attention was tested using the standardized d2-R test (Brickenkamp et al., 2010). Here, participants had to mark as many targets (d's with exactly two

dashes placed above or under the d) as possible within 14 rows containing d and p letters. After 20 s, participants had to switch to the next row. Following to the test manual, the first and last row were not included into the analysis. After 4.6 min the task was completed. KL (i.e., concentration) is calculated by subtracting false positives and omissions from the total amount of marked items.

Executive functioning was tested using the trail making test (TMT; Reitan, 1992). First, participants had to connect circles containing numbers as fast as possible into the right order (e.g., 1-2-3-4). Subsequently, circles containing numbers and letters had to be connected in alternating order (e.g., 1-A-2-B-3-C). For further analysis, the required time for both variations were summed up.

3.2.3 Image acquisition

Structural MRI was performed at the University of Lübeck using a 3T Siemens Magnetom Skyra scanner equipped with a 64-channel head coil. Whole-brain MPM was acquired as reported in previous studies (Weiskopf et al., 2013) using multi-echo 3D fast low angle shot (FLASH) at 1 mm isotropic resolution. The volumes were acquired for T1, PD, and MT weightings. The weightings differed in TE, TR, and flip angles. T1-weighted: six echo times (TE = 2.2, 4.7, 7.2, 9.7, 12.2, 15 ms), TR = 19 ms, flip angle = 20°; PD-weighted: eight echo times (TE = 2.2, 4.7, 7.2, 9.7, 12.2, 15, 17.5, 20 ms), TR = 24 ms, flip angle = 6°; MT-weighted: six echo times (TE: 2.2, 4.7, 7.2, 9.7, 12.2, 15 ms), TR = 37 ms, flip angle = 6°. A Gaussian MT-pulse following Siemens product sequences was applied. To shorten the scan duration, a partial Fourier 6/8 was used. Parallel imaging with a GRAPPA acceleration factor of 2 was applied. The total scanning time of the MPM protocol was approx. 20 min. Subsequently, two runs of diffusion weighted imaging (DWI) using an EPI sequence were performed during the same scanning session (scanning time approx. 16 min). The images were later used for further analysis (results will be reported elsewhere).

MR data were further processed on the Statistical Parametric Mapping framework (SPM 12, Wellcome Trust Center for Neuroimaging, London) and MATLAB software (R2014b version, Mathworks). R2* maps were calculated through a regression of the log signal from the PD-weighted echoes. Averaging the set of echoes for each weighting increased the signal-to-

noise-ratio for estimation of the MT map (Helms and Dechent, 2009). The semiquantitative MT map was calculated as described by Helms et al. (Helms et al., 2008a, 2008b). Subsequently, to ensure uniform orientations, images were slightly manually re-orientated according to individual posture during the MRI acquisition using SPM Check Reg and Display options (Ashburner, 2015).

3.2.4 Voxel-based morphometry and voxel-based quantification

GM volumes were processed and analyzed following a protocol for VBM using SPM's batch system (Ashburner and Friston, 2000; Ashburner, 2015). Since MT maps provide increased contrast for subcortical regions (Helms et al., 2009; Lorio et al., 2014), in a first step, they were used for segmentation of the different tissue groups. Subsequently, images of GM, WM, and CSF were generated in native space (Ashburner and Friston, 2005). Applying high dimensional warping, images were then normalized to MNI space using the DARTEL algorithm implemented in SPM, scaled by the Jacobian determinants of the deformation field and smoothed with an isotropic Gaussian Kernel of 6 mm FWHM. Finally, the resulting smoothed, modulated and normalized GM images were used for statistical analysis.

VBQ analysis provides sensitivity to tissue microstructure and is therefore well suited to test differences in R2* and MT, which are sensible marker for alterations in subcortical brain regions. VBQ was processed using the open source hMRI toolbox (Tabelow et al., 2019) embedded in the SPM framework. Using the integrated processing pipeline of the toolbox, the previously generated MT maps were further processed using the modules tissue segmentation (GM, WM, and CSF), DARTEL, creation of templates, and normalization to MNI space. Subsequently, tissue-weighted smoothing with a FWHM isotropic Gaussian kernel of 3 mm (Draganski et al., 2011) was performed. Resulting images of R2* and MT for GM were used to indirectly test for differences in iron levels (i.e., R2*) and myelination (i.e., MT) of brain tissue (see also Draganski et al., 2011; Callaghan et al., 2014). Note that we did not analyze WM subspace, since we focused on the BG structures that typically do not contain much WM (Lanciego et al., 2012). Moreover, the estimation of iron concentrations in WM regions (on the basis of quantitative susceptibility mapping) appears to be less accurate (Langkammer et al., 2012b). Analyses of MTR within GM structures have been related to demyelination (Chen et al.,

2013) and cognitive impairment (Kabani et al., 2002), suggesting a link between behavior and MT integrity of subcortical structures.

3.2.5 Manual segmentation of the SN/VTA

The SN/VTA is a fairly small subcortical structure and inter-individual differences of the SN/VTA boundaries can account for inaccuracy when applying normalized anatomical masks. Therefore, in the present study, a voxel-based ROI analysis in native space was conducted. Following previous studies (Bunzeck et al., 2007; Düzel et al., 2008) and using MRIcron tools, individual SN/VTAs were segmented based on the intense contrast change between the bright grey color and the dark grey color of the adjacent tissue in the MT-weighted image (**Figure 3.1**). The upper limit of the SN/VTA-ROI was selected at a level of the superior colliculi. The anterior part of the SN/VTA-ROI was limited by the interpeduncular fossa and posterior borders were limited by the lateral side of the cerebral peduncle. The lower limit of the SN/VTA-ROI was identified as the last even grey colored cross-sectional area. The total rostrocaudal extension of the ROI included approx. 10 slices depending on the individual size of the SN/VTA.

All segmentations were performed twice by one person. Only the latter segmentations were used for further analyses. Subsequently, the ROIs were extracted and projected as an overlay on the corresponding MT and R2* images to obtain the mean values (see also Düzel et al., 2008; Chowdhury et al., 2013). Reliability of the segmentation was tested with an intra-class correlation coefficient (ICC; Shrout and Fleiss, 1979) using IBM SPSS Version 24. There were significant correlations between the first and the second manual segmentation regarding values for MT (ICC= 0.978, $p < 0.001$) and R2* (ICC = 0.993, $p < 0.001$), suggesting high intra-rater reliability.

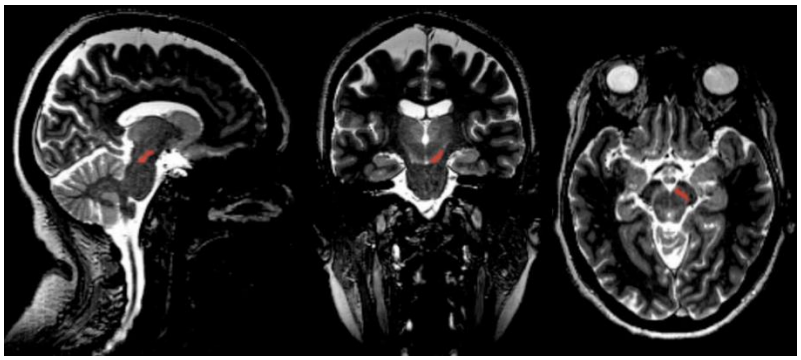

Figure 3.1. Manual segmentation of an individual SN/VTA. Within the midbrain, the SN/VTA can be identified as bright stripe on MT-weighted images. Bilateral SN/VTAs were defined as ROIs, which were used to quantify mean MT and R2* values. For illustration purposes, only the right SN/VTA is marked in red (i.e., ROI).

3.2.6 Statistical analysis

Participants with more than 3 standard deviations (SD) above or below the overall mean of a specific neuropsychological test were excluded from the respective analysis. For analyses of the relationship between microstructure and cognitive functioning, multiple regression analyses for VBM and VBQ were calculated with SPM using Matlab software. Covariates were age, LPS 50+, MWT, VLMT learning, VLMT cons, VLMT free recall, digit span, and d2-R. Due to one missing value in the VLMT recognition test and two outliers (> 3 SD) in the TMT, two additional linear regression analyses of VBM and VBQ were conducted for age and VLMT recognition, and age and TMT. Effects within subcortical regions of interest were investigated using a small volume correction (SVC) with a BG mask (i.e., caudate, pallidum, putamen, NAcc). The mask was taken from the Harvard-Oxford-Atlas (50% probability mask), implemented in the FMRIB Software Library (FSL; Jenkinson et al., 2012). Clusters with at least 50 voxels and a $p < 0.05$ after familywise error correction (FWE) at the cluster level ($p < 0.001$ uncorrected at peak-voxel level) were regarded as significant. For post hoc analyses and depictions of effects, MT and R2* values were extracted from significant brain regions (see results). To further examine effects of age on cognition, a post hoc partial correlation for age was applied for significant results of the VBM and VBQ analyses.

Finally, SN/VTA values (MT and R2*) and their relationship to cognitive performance were investigated using a correlation analysis in SPSS. MT and R2* values were averaged across voxels for each individual SN/VTA-ROI (see above). The correlation analysis of the structural

parameter (MT, R2*), age and the neuropsychological tests was Benjamini-Hochberg (FDR) corrected.

Not all data were normally distributed; however, due to the large sample size (79 participants), our inferential statistics are supposed to be robust against a violation of the assumption of normality (i.e., central limit theorem; Field, 2017).

3.3 Results

3.3.1 VBM analysis

VBM multiple regression analyses with GM as dependent variable were performed to test for correlations with age and cognitive performance, respectively (cluster level FWE, $p < 0.05$; note that for VLMT recognition and TMT separate analyses had to be performed, see methods). A SVC using a BG mask revealed a negative relationship between age and GM volume within the right caudate, pallidum, and putamen (**Table 3.1**; **Figure 3.2a-b**), and a positive correlation between GM volume and VLMT recognition in the caudate (**Table 3.1**). There were no further significant correlations between GM and behavior. When adding age as a covariate (i.e., post hoc partial correlation), the effect between GM volume and VLMT recognition only reached trend level ($r = 0.208$, $p = 0.07$).

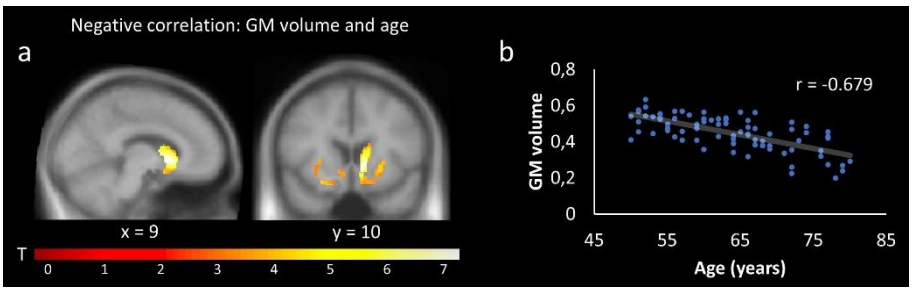

Figure 3.2. Negative relationship between age and GM volume. **a.** SPM showing a significant negative relationship between GM volume and age within the right caudate, pallidum, and putamen; **b.** showing the corresponding correlation plot for the cluster. For display purposes, SPMs were thresholded at $p < 0.001$, uncorrected, and superimposed on the mean T1-weighted image.

3.3.2 VBQ analysis on R2*

VBQ multiple regression analyses with GM R2* were performed (note that for VLMT recognition and TMT separate analyses had to be performed, see methods). The analysis showed a significant positive effect between age and R2* within the left and right putamen (SVC, cluster level FWE, $p < 0.05$; **Table 3.1**; **Figure 3.3a**). Post hoc, MT and R2* values were extracted from that cluster for further analyses. As expected, there was a significant positive correlation between age and GM R2* ($r = 0.475$; **Figure 3.3b**), a negative correlation between age and GM MT ($r = -0.656$, $p < 0.001$; **Figure 3.3c**), and a negative correlation between GM MT and GM R2* ($r = -0.339$, $p = 0.002$; adjusted alpha level: 0.05/3 = 0.016; **Figure 3.3d**). However, when adding age as covariate in a subsequent partial correlation, the relationship between GM MT and GM R2* no longer remained significant ($r = -0.042$, $p = 0.717$).

Regarding behavioral performance, GM R2* correlated negatively with performance in VLMT recognition (i.e., left and right putamen) and free recall (i.e., left and right putamen/pallidum) – cluster level FWE-corrected, $p < 0.05$ (**Table 3.1**; **Figure 3.4a-b**). Furthermore, GM R2* of the left and right putamen correlated positively with the TMT (higher values [s] in the TMT imply worse performance; **Table 3.1**; **Figure 3.4c-d**). There were no other significant effects with regard to R2*. When adding age as a covariate in a post hoc partial correlation, the effects remained significant (GM R2* and VLMT recognition: $r = -0.400$, $p < 0.001$; GM R2* and TMT: $r = 0.240$, $p = 0.041$).

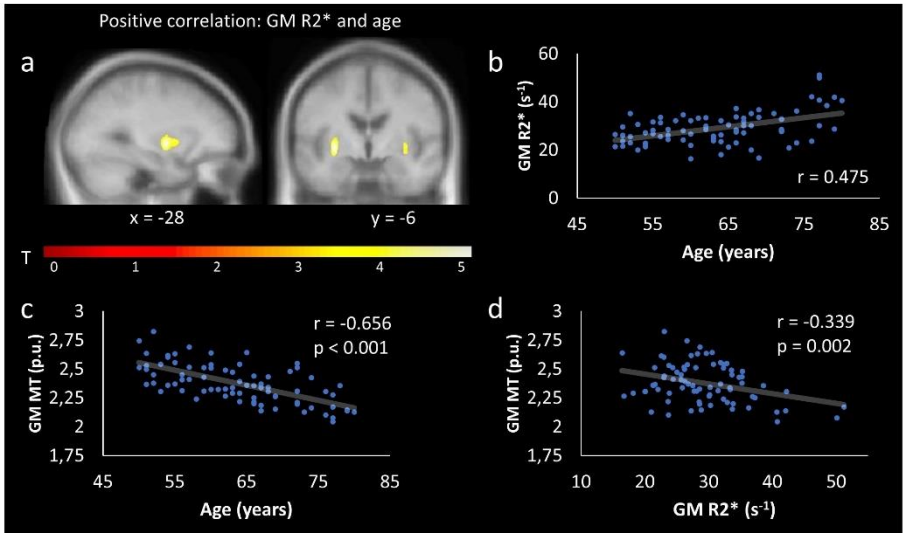

Figure 3.3. Positive relationship between age and GM R2*. **a.** SPM showing a significant positive relationship between GM R2* and age within the left and right putamen; **b.** shows the corresponding correlation plot for the cluster. For post hoc analyses, GM MT values were extracted from the same cluster. They revealed a negative relationship between GM MT and age (**c**), and a negative relationship (not corrected for age) between GM R2* and GM MT (**d**). For display purposes, SPM was thresholded at p < 0.001, uncorrected, and superimposed on the mean T1-weighted image.

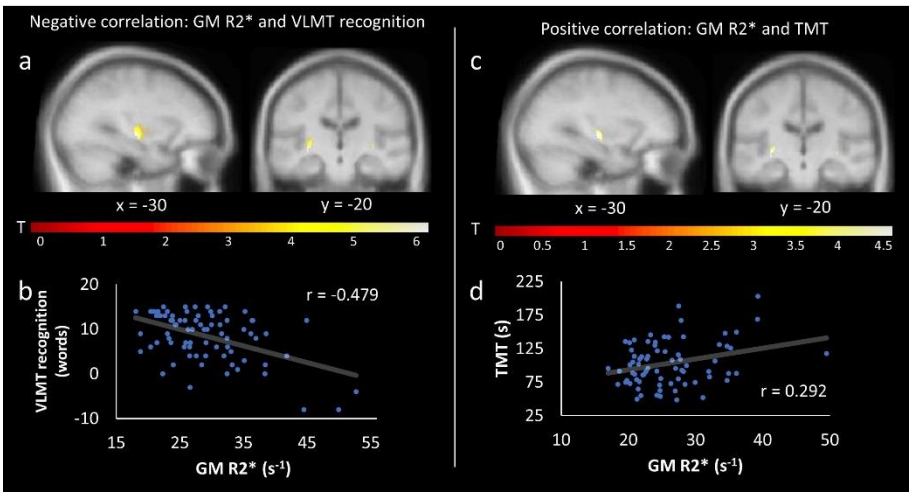

Figure 3.4. Relationship between cognitive performance and GM R2*. SPMs showing a significant negative relationship between GM R2* and VLMT recognition within the left and right putamen (**a**); a positive relationship between GM R2* and TMT within the left and right putamen (**c**). The corresponding correlation plots are shown in **b**, **d**. In **d** three outliers were removed from the post hoc analysis (R2* values > 3 SD). For display purposes, SPMs were thresholded at p < 0.001, uncorrected, and superimposed on the mean T1-weighted image.

3.3.3 VBQ analysis on MT

VBQ multiple regression analyses on GM MT revealed negative correlations between age and MT within the BG (SVC) (note that for VLMT recognition and TMT separate analyses had to be performed, see methods). Three clusters within the caudate and pallidum were identified (**Table 3.1**; **Figure 3.5a-b**).

Regarding cognitive performance, GM MT correlated positively with VLMT recognition (**Table 3.1**; **Figure 3.5c-d**) and GM MT in the left pallidum correlated positively with VLMT free recall (**Table 3.1**). Additionally, GM MT within the caudate, putamen, and pallidum correlated negatively with the TMT (higher values [s] in the TMT imply worse performance; **Table 3.1**; **Figure 3.5e-f**). In a post hoc partial correlation with age as a covariate, all correlations remained significant (GM MT and VLMT recognition: r = 0.276, p = 0.015; GM MT and TMT: r = -0.274, p = 0.017).

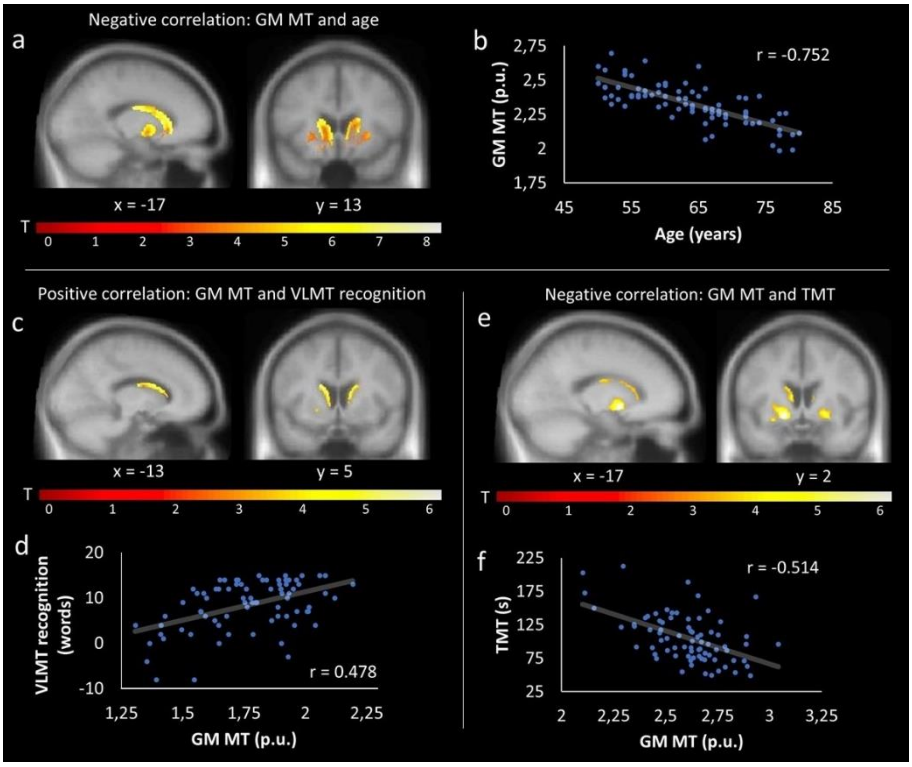

Figure 3.5. Relationship between GM MT, age, and cognitive performance. SPMs showing a significant negative relationship between GM MT and age within left and right caudate (**a**); a positive relationship between GM MT and VLMT recognition within the left and right caudate (**c**); and a negative relationship between GM MT and TMT within the left and right pallidum (**e**). The corresponding correlation plots for the clusters are shown in **b**, **d**, **f**. For display purposes, SPMs were thresholded at p < 0.001, uncorrected, and superimposed on the mean T1-weighted image.

Table 3.1. Results of VBM and VBQ. Table shows results of VBM and VBQ (on R2* and MT GM) multiple regressions. Positive effects (one sided) are marked with a (+) and negative effects with a (-). P-values correspond to the cluster (FWE corrected) and the MNI coordinates to the respective peak voxel. Note that for VLMT recognition and the TMT separate regression analyses were performed (see text).

Analysis	Side	Region	p-value (FWE-corrected)	Number of voxels k	MNI coordinates (mm) x	y	z
			GM volume				
Age (-)	R	Caudate	<0.001	2132	9	10	2
VLMT recognition (+)	R	Caudate	0.047	709	18	-21	22
			*GM R2**				
Age (+)	L	Putamen	<0.001	766	-28	-6	0
	R	Putamen	<0.001	544	28	0	2
VLMT recognition (-)	L	Putamen	<0.001	1213	-30	-20	-2
	R	Putamen	<0.001	998	30	-17	-3
VLMT free recall (-)	L	Putamen/Pallidum	0.001	168	-20	-6	6
	R	Putamen/Pallidum	<0.001	450	23	-11	5
TMT (+)	L	Putamen	<0.001	194	-30	-20	-1
	L	Pallidum	0.003	153	-19	-10	1
	R	Putamen	0.001	189	32	-17	-3
			GM MT				
Age (-)	L	Caudate	<0.001	10552	-17	13	6
	R	Caudate	<0.001	2793	9	5	11
	R	Pallidum	<0.001	6219	23	-3	2
VLMT recognition (+)	L	Caudate	<0.001	1633	-13	5	21
	R	Caudate	<0.001	1603	13	20	11
	L	Pallidum	0.001	133	-19	0	-5
VLMT free recall (+)	L	Pallidum	0.04	73	-16	-4	-3
TMT (-)	L	Pallidum	<0.001	1901	-17	2	-3
	L	Caudate	<0.001	1670	-13	5	21
	L	Putamen	0.001	136	-21	11	-2
	L	Putamen	0.013	92	-29	-11	0
	R	Pallidum	<0.001	721	20	2	-2
	R	Caudate	0.005	106	14	-9	19
	R	Caudate	<0.001	157	10	8	16

3.3.4 Analysis of the SN/VTA in native space

In a last step, individually defined ROIs for the SN/VTA in native space were used to extract MT and R2* values for each subject (mean MT [p.u.] = 2.2 ± 0.174; mean R2* [s^{-1}] = 23.4 ± 4.01). A correlation analysis between age, R2*, MT, and each neuropsychological test revealed a negative relationship between age and MT within the SN/VTA (r = -0.348, FDR adjusted p = 0.01; **Figure 3.6a**), but not between age and R2* (r = 0.031, FDR adjusted p = 0.787; **Figure 3.6b**) or MT and R2* (r = 0.184, FDR adjusted p = 0.21; **Figure 3.6c**). Furthermore, age correlated negatively with LPS 50+, VLMT learning, VLMT free recall, and VLMT recognition, d2-R, and TMT. Finally, a positive correlation between SN/VTA R2* and TMT reached trend level (FDR adjusted p = 0.06; **Table 3.2**) – note that higher values (s) in the TMT imply worse performance.

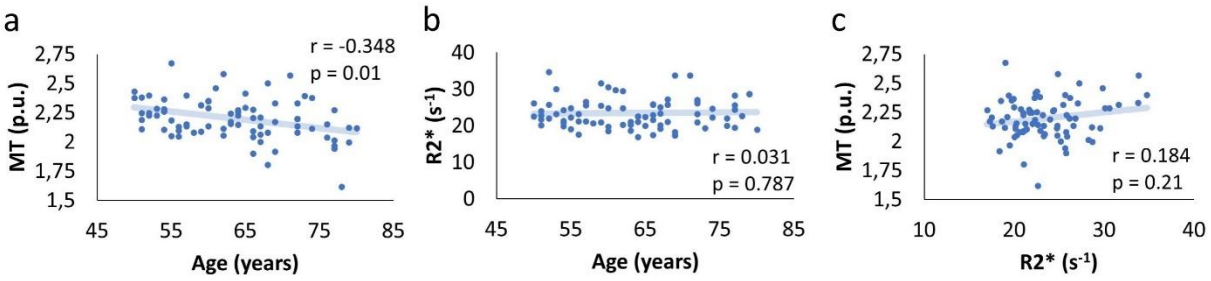

Figure 3.6. Relationship between MT, R2*, and age within the SN/VTA. We observed a significant negative correlation between MT and age (**a**); but no significant correlations between (**b**) R2* and age or (**c**) MT and R2* ($p > 0.05$). Benjamini-Hochberg (FDR) p-value adjustment was applied.

Table 3.2. Correlation matrix for SN/VTA parameters. Age, R2*, and MT were correlated with each neuropsychological test (Pearson correlation). Benjamini-Hochberg (FDR) p-value adjustment was applied. Significant results are highlighted with an asterisk. Note that there was one missing value for VLMT recognition and that two participants had to be removed from the TMT analysis (> 3 SD, see text).

		Age	R2*	MT
Age	r	-		
	p-value	-		
R2*	r	0.031	-	
	p-value	0.787	-	
MT	r	-0.348	0.184	-
	p-value	0.01*	0.21	-
MWT	r	0.123	-0.064	-0.137
	p-value	0.367	0.614	0.362
LPS 50+	r	-0.328	-0.093	0.126
	p-value	0.013*	0.479	0.383
VLMT learning	r	-0.432	-0.120	0.159
	p-value	<0.001*	0.366	0.284
VLMT cons	r	0.228	0.048	-0.094
	p-value	0.143	0.697	0.493
VLMT recall	r	-0.418	-0.172	0.194
	p-value	<0.001*	0.244	0.199
VLMT recognition	r	-0.416	-0.225	0.187
	p-value	<0.001*	0.141	0.216
Digit span	r	-0.220	-0.146	0.081
	p-value	0.14	0.33	0.53
d2-R	r	-0.456	-0.124	0.203
	p-value	<0.001*	0.375	0.183
TMT	r	0.489	0.274	-0.129
	p-value	<0.001*	0.06	0.396

3.4 Discussion

We investigated age-related differences in GM and microstructural markers of myelin (i.e., MT) and iron (i.e., R2*) levels within the BG and their link to cognitive performance. In line with our hypotheses, cognitive performance negatively correlated with age in most tests. At the neural level, we observed age-related declines of GM volume and MT, and an increase of R2* relative to the tested age range. Importantly, performance in verbal memory and executive function was predicted by MT (positive relationship) and R2* (negative relationship). Finally, a ROI-analysis of the SN/VTA revealed age-related demyelination (as indicated by MT) but no clear link between behavior and R2* or MT, respectively. As such, our findings are compatible with the role of the BG in multiple cognitive functions, and they give new insights into the specific functional consequences of age-related microstructural changes.

Neural degeneration within the BG is typical for heathy aging (Callaghan et al., 2014; Hafkemeijer et al., 2014; Bauer et al., 2015), and might reflect a loss of neuronal and dendritic architecture, rather than a loss of neurons (Esiri, 2007; Freeman et al., 2008). Although the underlying processes are still unclear, microstructural changes and oxidative damage might be of particular relevance (see as review Esiri, 2007). Indeed, apart from GM reductions, our findings show that MT negatively correlated with age within the caudate, putamen, and pallidum (**Figure 3.5a-b**). This presumably indicates less macromolecular content (e.g., oligodendrocytes) and might reflect demyelinating processes (Peters, 2002; Sled, 2018). A positive correlation between age and R2* within the putamen were accompanied by a negative relationship to MT (**Figure 3.3**). This is in accordance with previous studies (Steiger et al., 2016), and may indicate a dysfunction of myelin-forming oligodendrocytes, which are sensitive to oxidative stress (Peters, 2002), possibly triggered by increased iron levels (Connor, 2004; Daugherty and Raz, 2015). Importantly, the negative relationship between R2* and MT did not remain significant when controlling for age in a partial correlation, suggesting that the interplay between iron and demyelination is not independent from age. Therefore, future studies should further investigate the relationship between all three factors ideally in a longitudinal design.

With regard to behavior, we can confirm our hypothesis (Daugherty et al., 2015; Steiger et al., 2016) by demonstrating a negative relationship between R2* and verbal memory

performance within the putamen/pallidum (**Table 3.1**; **Figure 3.4a-b**). In order to encode novel information into LTM, the hippocampal VTA-loop model suggests that a hippocampal novelty signal is sent to the DA neurons within the SN/VTA via a polysynaptic path including the subiculum, NAcc, and ventral pallidum before DA neurons back-project to the hippocampus (Lisman and Grace, 2005; Lisman et al., 2011). While iron is required for DA synthesis (Zecca et al., 2004), an accumulation of it can impair DA production (Zecca et al., 2004; Hare and Double, 2016). Therefore, increased iron levels within the bilateral putamen/pallidum may account for an imbalance of the loop, leading to impairments in verbal memory.

Importantly, while previous work has already demonstrated a relationship between striatal iron and episodic memory (Daugherty et al., 2015; Steiger et al., 2016; Kalpouzos et al., 2017), our findings show that iron accumulation (as indicated by R2*) within the BG also impact on executive functioning in healthy older adults (**Figure 3.4c-d**). Psychological models of executive functioning typically include several mental processes, such as planning, task switching, inhibition, and cognitive flexibility (see e.g., Diamond, 2013). At the neural level, executive processing is strongly related to the medial frontal lobe (Alvarez and Emory, 2006), but there is also a body of evidence for a close link to the fronto-striatal circuit (Volkow et al., 1998; Rubin, 1999; Bäckman et al., 2000; Buckner, 2004; Leh et al., 2010). Notably, in Parkinson's disease, which is characterized by increased iron levels within the SN/VTA, red nucleus, putamen, pallidum, and caudate (e.g., Wang et al., 2016), executive dysfunction is already present in early stages of the disease (Muslimovic et al., 2005; Uc et al., 2005). It has been suggested that executive disorders in Parkinson's disease originate from DA depletion within the striatum, resulting in a dysfunction of the fronto-striatal circuit (Grahn et al., 2008; Leh et al., 2010; de la Fuente-Fernández, 2012). More evidence comes from a PET study testing patients with mild Parkinson's disease and healthy controls on a typical planning task (Tower of London). While both groups showed overlapping task-related activation patterns within the PFC, only healthy controls showed activation within the right caudate. In contrast, in patients with Parkinson's disease, activation within the right hippocampus was increased, suggesting a compensatory shift towards the declarative memory network (Dagher et al., 2001). Therefore,

increases in BG iron levels during healthy aging may impair fronto-striatal circuits, leading to reduced executive functioning.

Verbal memory and executive functioning could also be predicted on the basis of BG myelination (as indicated by MT; **Figure 3.5c-f**). At the physiological level, age-related reduction of myelin may impair saltatory conduction at the nodes of Ranvier and thereby, decreased velocity of action potentials along the myelin sheaths (Nave and Werner, 2014; Freeman et al., 2016). This, in turn, could impair behavior – in our case verbal memory and executive functioning. Indeed, previous studies could demonstrate that myelin facilitates learning processes (see as a review Sampaio-Baptista and Johansen-Berg, 2017), while demyelination is related to a deceleration of processing speed in healthy aging (Chopra et al., 2018). Moreover, in MCI, demyelination is found within several brain regions (Carmeli et al., 2013; Bouhrara et al., 2018).

In the present study, we observed a negative correlation between age and GM volume within the right caudate, pallidum, and putamen (**Figure 3.2a-b**), and a (weak) link between GM volume and verbal memory (i.e., VLMT recognition) in particular within the caudate nucleus. This is in line with previous work on age-related structural degeneration of the BG (Raz et al., 2003; Hafkemeijer et al., 2014; Bauer et al., 2015), and notion of a close relationship between caudate volume and associative memory (Bauer et al., 2015), intelligence (Grazioplene et al., 2015), cognitive flexibility (Verstynen et al., 2012), and learning (Tricomi et al., 2006). However, it should be noted that the relationship between GM volume and VLMT recognition was only borderline significant ($p=0.07$) when adding age as covariate in a partial correlation. Again, this suggests that the interplay between BG volume and verbal memory is not independent from age.

A ROI-analysis of the SN/VTA revealed a significant negative correlation between age and MT, but no significant effect between age and R2* (**Figure 3.6**). These observations are compatible with previous studies in healthy older adults, which also indicate age-related MT decreases (Düzel et al., 2008; Chowdhury et al., 2013) but no significant changes in iron (Zecca et al. 2001). With regard to the pattern observed in the BG, this suggests that, during healthy aging, myelin decreases are typical in both regions (BG and SN/VTA), whereas iron increases

are only typical within the BG but not SN/VTA. Interestingly, in patients with Parkinson's disease, iron increases have been reported in the BG and SN/VTA (Wang et al., 2016). This suggests that BG iron increases as well as demyelination in the BG and SN/VTA are typical for healthy aging, whereas SN/VTA iron levels are specific to pathologic neurodegeneration (Zecca et al., 2004; Toulorge et al., 2016). However, since only older adults have been tested here (50-80 years), we cannot exclude the possibility that a group of young controls might have shown significantly lower iron levels in the SN/VTA.

Despite a significant relationship between age and demyelination (as indicated by MT) of the SN/VTA, there was no clear link between structural integrity (MT or R2*) and behavior (**Table 3.2**). The only hint was based on a negative correlation between R2* and executive function (TMT, uncorrected $p = 0.016$), but this did not survive Benjamini-Hochberg correction (adjusted $p = 0.06$). This absence is in contrast to previous work on SN/VTA integrity in healthy older adults demonstrating a link between MTR and verbal memory (Düzel et al., 2008), MT and reward-related reaction times (Steiger and Bunzeck, 2017) as well as MT and learning in a go-no-go-task (Chowdhury et al., 2013). These apparently divergent findings may relate to differences in MR data-acquisition protocols or differences in cognitive/behavioral readouts and they may suggest that the relationship between SN/VTA integrity and behavior may be modulated by other factors that were not explicitly included in our analysis (e.g., personality traits).

Along the same lines, hypertension and vascular diseases may also relate to the brain's microstructure and cognitive functioning. Indeed, hypertension is one of the main risk factors for stroke (Kuźma et al., 2018) and small vessel disease (Bos et al., 2018), both strongly linked to dementia (Hörnsten et al., 2016; Boehme et al., 2017; Jiménez-Balado Joan et al., 2019). Moreover, education (Chen et al., 2019) and lifestyle factors (Atallah et al., 2018) have been shown to account for inter-individual differences in healthy aging. Therefore, future studies should more thoroughly take these factors into account.

Finally, our findings must be interpreted with several limitations. First, MT and R2* are only indirect makers of myelin and iron contents and therefore, should be interpreted with caution (e.g., Daugherty and Raz, 2015). However, post mortem studies provide histological

evidence for a strong relationship between MT and myelin (Schmierer et al., 2004) as well as R2* and iron (Langkammer et al., 2010). Along the same lines, R2* is sensitive to both, iron and myelin (Lodygensky et al., 2012; Kor et al., 2019) but previous work suggests that the correlation between R2* and iron concentration in GM might be higher as compared to R2* and iron concentration in WM (Langkammer et al., 2010). In any case, the interpretation of R2* is not only indirect but also complex (see e.g., Langkammer et al., 2012b, 2012a). Second, VBM might be vulnerable to include voxels of WM, CSF, or blood vessels and can, therefore, confound estimates of R2* and MT (see Scarpazza et al., 2015). Manual segmentation of the SN/VTA, on the other hand, might have been biased by iron concentration (Lorio et al., 2014). Third, we would like to point out that the current study followed a cross-sectional but no longitudinal approach. Therefore, terms like "increase" or "decrease" relate to between-subjects comparisons within the age range of our sample but they do not imply individual development over time. Moreover, multiple regression analyses, as used here, do not speak to causality and specificity. In other words, we can show that age, iron levels, and demyelination predict (in a statistical sense) cognitive functions, but our design and analyses cannot pinpoint directionality, and conclusions with regard to unique effects of each factor are limited. A further specification of each modality (R2*, MT, volume) and brain region would require another complex and multivariate model, which we have not employed here, but might be addressed in future studies.

To summarize, age-related markers of iron levels and demyelination within the BG were correlated, which is in line with the role of iron in dysfunctional myelin synthesis. Importantly, iron levels and demyelination predicted both verbal LTM and executive functioning, which gives novel insights into the behavioral consequences of BG microstructural changes. From a more general perspective, our results further suggest that increased iron and demyelination within the BG are typical for healthy aging and they might be distinguished from age-related differences in SN/VTA microstructure.

4 Study 2: The gains of a 4-week cognitive training are not modulated by novelty

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Abstract

Cognitive training should not only improve performance of the trained task, but also untrained abilities. Exposure to novelty can improve subsequent memory performance, suggesting that novelty exposure might be a critical factor to promote the effects of cognitive training. Therefore, we combined a 4-week working memory training with novelty exposure. Neuropsychological tests and MRI data were acquired before and after training to analyze behavior and changes in grey matter volume, myelination, and iron levels. In total, 83 healthy older humans participated in one of three groups: two groups completed a 4-week computerized cognitive training of a 2-back working memory task, either in combination with novel or with familiarized nature movies. A third group did not receive any training. As expected, both training groups showed improvements in task specific working memory performance and RTs. However, there were no transfer or novelty effects on fluid intelligence, verbal memory, digit-span, and executive functions. At the neural level, no significant micro- or macrostructural changes emerged in either group. Our findings suggest that working memory training in healthy older adults is associated with task-specific improvements, but these gains do not transfer to other cognitive domains, and it does not lead to structural brain changes.

4.1 Introduction

In healthy older humans, cognitive abilities can be improved by cognitive training. While specific training gains appear to underline the brain's plasticity throughout the life-span (Heinzel et al., 2014), some cognitive trainings go even further by demonstrating a transfer to untrained cognitive abilities (so-called transfer effects). For instance, working memory trainings not only improved performance of the trained task (i.e., training gains), but they also improved fluid intelligence (Jaeggi et al., 2008), verbal memory (Richmond et al., 2011), executive functions (Heinzel et al., 2016) and processing speed (Heinzel et al., 2016) (i.e., transfer effects). Along the same lines, effects of trainings that are based on video games have been shown to transfer to executive functions (Nouchi et al., 2012), processing speed (Nouchi et al., 2012), and working memory (Anguera et al., 2013). However, evidence in favor of transfer effects is equivocal and, therefore, the underlying processes remain unclear.

At the neural level, cognitive training has been associated with functional and anatomical effects. For instance, trainings can lead to increased DA release (Bäckman et al., 2017), increased striatal BOLD activity (Dahlin et al., 2008) and reduced hemodynamic activity in frontal brain regions (Heinzel et al., 2016). Interestingly, working memory training gains in older adults were most pronounced in those participants showing a pre-test neural activity pattern that was similar to the one observed in younger controls (Heinzel et al., 2014), suggesting that inter-individual variability may play an important role (see also Buitenweg et al., 2012). Moreover, a multi-task video game led to functional changes in midline frontal theta (4-7 Hz) power and long-range theta coherence as measured with EEG (Anguera et al., 2013). With regard to anatomical changes, increases in cortical thickness of frontal brain regions (i.e., left orbitofrontal cortex, right lateral orbitofrontal cortex, fusiform cortex) (Engvig et al., 2010), and a preserved fractional anisotropy (FA; an indicator for the degree of restrictiveness of water molecules) of frontal WM (Engvig et al., 2012) were reported. Similarly, the amount of working memory training correlated with FA increases in regions adjacent to the intraparietal sulcus and anterior part of the body of the corpus callosum (Takeuchi et al., 2010) further suggesting a role of inter-individual differences in training gains and transfer effects.

Despite the above mentioned reports, several studies could not show a transfer of training gains to other domains (Owen et al., 2010; Shipstead et al., 2010; Redick et al., 2013). While this may have several reasons, it appears obvious that the exact mechanisms and conditions under which transfer effects occur remain unclear. However, since striatal activity (Dahlin et al., 2008) and DA release within striatal areas (Bäckman et al., 2017) increase after working memory training, a positive effect to other domains that depend on striatal integrity seems feasible. In fact, the striatum is not only vital for working memory, but also associative memory (Bauer et al., 2015), learning (Foerde and Shohamy, 2011), verbal memory (Steiger et al., 2016), executive function (Leh et al., 2010), and fluid intelligence (Rhein et al., 2014). Therefore, working memory training could have a positive effect on the dopaminergic circuit and therefore, enhance performance in the aforementioned cognitive domains.

Here, on the basis of a possible link between dopaminergic neuromodulation and training effects (Dahlin et al., 2008; Bäckman et al., 2017), we investigated whether novelty, which is also associated with DA release and synaptic plasticity, promotes training gains and transfer effects (Buitenweg et al., 2012). Indeed, novel information is supposed to activate a loop between the medial temporal lobe (MTL) and DA neurons of the SN/VTA (Lisman and Grace, 2005; Lisman et al., 2011). Specifically, a novelty signal is generated within the MTL, which is transmitted to SN/VTA neurons via a polysynaptic path. The SN/VTA, in turn, back projects to the MTL, where DA drives synaptic plasticity, learning and memory processes. Evidence for such a loop has been provided by several studies in animals (reviewed in Lisman and Grace, 2005; Lisman et al., 2011) and, more recently, also humans (Bunzeck and Düzel, 2006; Wittmann et al., 2007; Bunzeck et al., 2014). At the behavioral level, the presentation of novel images and the exposure to a novel VR before a word-learning phase improve subsequent memory performance (Fenker et al., 2008; Schomaker et al., 2014) in humans. In animals, novelty exposure before and after the initial learning phase (Wang et al., 2010a) drives memory performance via dopaminergic processes (Li et al., 2003; Moncada and Viola, 2007; Ballarini et al., 2009; Wang et al., 2010a).

Therefore, training gains and transfer effects might be promoted by novelty and lead to structural brain changes within the dopaminergic mesolimbic system. In order to test this hypothesis, we combined a 4-week 2-back working memory training with the presentation of

novel nature movies (novelty group, NOV) or with the presentation of familiarized nature movies (familiarity group, FAM); a third passive control group did not receive any training task (CON). Before and after training, participants were assessed with a battery of neuropsychological tests (tapping into Gf and Gc, attention and processing speed, verbal and numeric memory, and executive functions) and a computerized train ticket machine (testing for a transfer to rather unrelated everyday abilities). Further, we used MRI based micro- and macrostructural measures of GM, myelination, and iron levels (Weiskopf and Helms, 2008; Draganski et al., 2011) before and after the training to further our understanding of the underlying neural processes. We had four major hypotheses: (a) training improves performance of the trained task (i.e., training gains: higher hit rates and faster RTs over time); (b) on the basis of previous studies with a very similar task (Heinzel et al., 2016), we expected significant transfer effects in tests for Gf, verbal and numeric memory, processing speed and executive function; (c) we expected changes in micro- and macrostructural integrity within mesolimbic brain regions; and (d) we expected these effects (a-c) to be enhanced by novelty. Additionally, we explored possible reasons for inter-individual differences, i.e., whether training gains and transfer effects relate to structural brain integrity at baseline and whether training gains further relate to personality traits (Big-Five) or baseline cognitive abilities (MoCA).

4.2 Materials and methods

4.2.1 Participants

In total, 92 healthy, right-handed, German speaking older adults were recruited. However, nine participants were excluded due to a history of neurological, psychological or other severe physical disorders, drug abuse, CNS affecting medication intake (less than 2 weeks before testing), non-removable metal implants or claustrophobia (for further details see **Figure 4.1**). Moreover, participants were excluded with > 5 points in the GDS (max. 15 points, > 5 points indicates mild depression; Sheikh et al., 1991) and < 22 points in the MoCA (max. 30 points; Nasreddine et al., 2005; Freitas et al., 2013). A value of 22 was chosen based on a study by Freitas et al. (2013), suggesting that it might be an appropriate cut-off for MCI. Finally, 83 older adults (mean age 63.93 ± 8.54, 39 females) were included in the sample and randomly assigned into two experimental (novelty – NOV, familiarity – FAM) and one passive control group (CON).

The NOV group included 28 participants (mean age 64.29 ± 9.69 years, 13 women, mean MoCA = 26.9 ± 1.91, 11.7 ± 1.54 mean years of school), the FAM group 28 participants (mean age 64.18 ± 8.10 years, 14 women, mean MoCA = 26.3 ± 2.16, 11.1 ± 1.88 mean years of school), and the CON group 27 participants (mean age 63.30 ± 7.99 years, 12 women, mean MoCA = 26.7 ± 2.18, 11.6 ± 1.6 mean years of school).

In total, 79 participants completed both MRI sessions and could, therefore, be included in further structural analyses. Finally, due to technical issues with one tablet, only the data of 55 instead of 56 training sessions were included in the analysis of the training task (**Figure 4.1**). All participants were recruited through local newspaper announcements or the database of the Institute of Psychology (Greiner, 2015). All participants signed a written informed consent and received monetary compensation: participants of the experimental groups (NOV and FAM) received 150 €, while participants of the CON group received only 60 €, since they were not participating in the 4-week training period. The study was approved by the local ethical committee of the University of Lübeck, Germany, and in accordance with the Declaration of Helsinki. This study was not a registered trial.

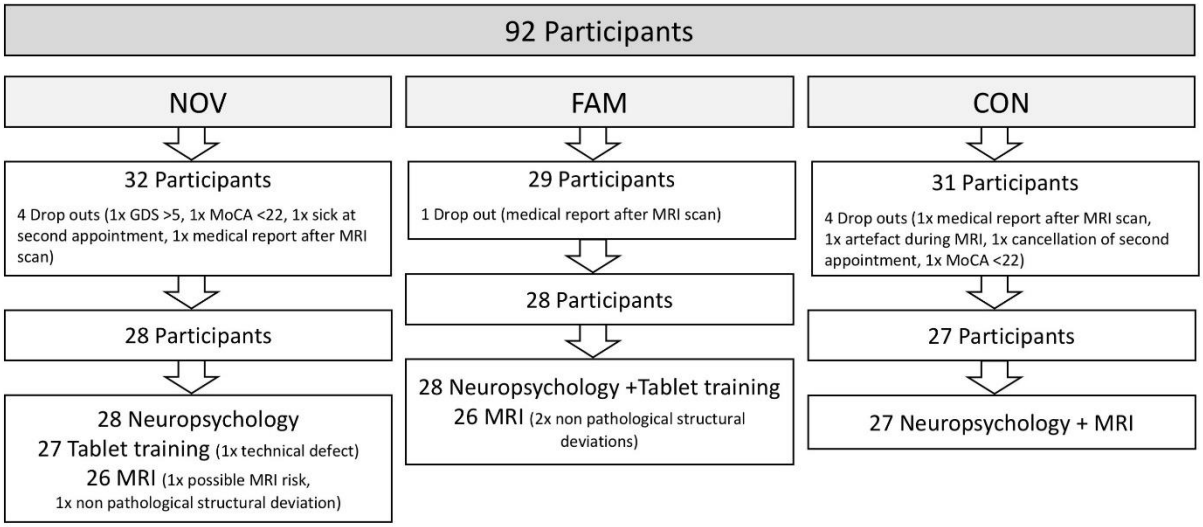

Figure 4.1. Flow chart of participant recruitment. Numbers indicate recruited participants, drop-outs and the final sample. Abbreviations: novelty group = NOV, familiarity group = FAM, control group = CON.

4.2.2 Experimental design and procedure

First, all participants received a baseline examination at the University of Lübeck. This included a detailed neuropsychological assessment (duration ~2 hours, see below) and a structural MRI scan (duration ~1 hour, see below). Subsequently, both experimental groups (NOV and FAM) were instructed on how to perform the working memory task (see below) and how to use the tablet computer, which was provided for the following four training weeks. The CON group did not train the working memory task and, therefore, did not receive further explanations in this regard. Finally, after four weeks, all participants returned and completed a second neuropsychological assessment and structural MRI (**Figure 4.2**).

Note, that participants of the experimental groups were not informed about the expected outcomes regarding different training manipulations (novel vs. familiar movies). Participants of the control group were informed that they were part of a control group; but, similar to the experimental groups, they were not informed about expected outcomes.

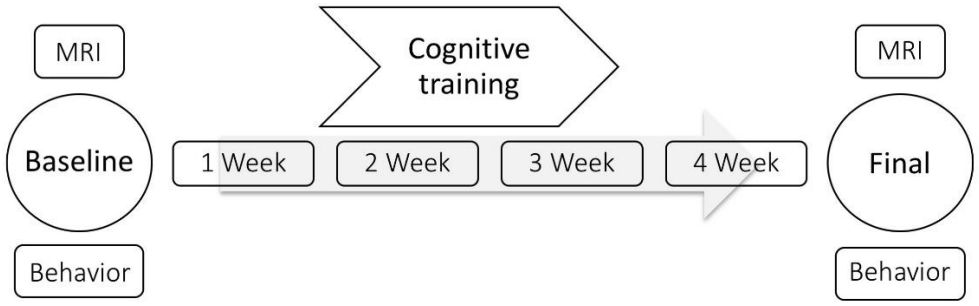

Figure 4.2. Experimental timeline. All participants completed a neuropsychological assessment and MRI measurements at baseline and four weeks after. Both experimental groups performed a 4-week cognitive training. The passive control group only attended at baseline and four weeks later for post-test measurements without participating in a training program.

4.2.3 Cognitive assessment

Neuropsychological tests were acquired at two time points: pre-training (t1) and post-training (t2). They tapped into Gf and Gc, verbal and numeric memory, processing speed, and executive functions. Gf was measured by the LPS 50+ short version (for people aged 50–90 years; Sturm et al., 2015), which includes a battery of time restricted paper pencil tasks (duration ~30 minutes). For Gc, the MWT (Lehrl et al., 1991; Lehrl, 1995) was applied; it provides 37 rows, each

containing four pseudo-words and one correct word, which has to be identified (with no time restriction).

Verbal memory was examined using the VLMT (Helmstaedter et al., 2001). Here, a word list of 15 nonrelated items was verbally presented for five subsequent times. Each time, participants were asked to recall as many words as possible. Recalled words were noted from the examiner (total sum of correctly recalled words of all five runs refers to VLMT learning in further analysis). In a sixth run, an interference list of 15 words was verbally presented, which had to be immediately recalled. Subsequently, participants were asked to recall words from the initial list (without further verbal presentation from the examiner). After 20 min (again without further verbal presentation), the initial word list had to be recalled (VLMT recall). Consolidation loss (VLMT cons) is calculated by subtracting the amount of words remembered in the fifth round from VLMT recall. Finally, a recognition task was conducted. Here, words of the initial list were intermixed with words of the interference list and new words. The list was read out aloud and participants had to judge whether they recognized a word from the initial word list or not (VLMT recognition).

Numeric short term memory (working memory) was assessed by using a digit span forward and backward test (Wechsler, 1987). Participants had to remember verbally presented digits in the same or reversed order. Correct recall increased the digit span by one number. Forward started with 3 digits and ended with 8 digits or after 2 errors within the same difficulty level; backward started with 2 digits and ended with 7 digits or after 2 errors within the same difficulty level.

Processing speed and attention was tested using the standardized d2-R test (Brickenkamp et al., 2010). Here, participants had to mark as many targets (d's with exactly two dashes placed above or under the d) as possible within 14 rows containing d and p letters. After 20 s, participants had to switch to the next row. Following the test manual, the first and last row were not included into the analysis. After 4.6 min, the task was completed. We analyzed BZO (i.e., working speed), which refers to the number of marked items, and KL (i.e., concentration), which represents the corrected BZO score (BZO – [false positive + omissions] = KL) and is therefore a more sensitive marker for processing speed.

Executive functioning was tested using the TMT (Reitan, 1992). First, participants had to connect randomly distributed circles containing numbers as fast as possible into the right order (TMT-A, sustained attention; e.g., 1-2-3-4). Subsequently, circles containing numbers and letters had to be connected in alternating order (TMT-B, divided attention; e.g., 1-A-2-B-3-C).

To assess possible influences of personality traits, a short version of the Big-Five inventory (BFI-10) with five levels covering extraversion, agreeableness, conscientiousness, neuroticism and openness to experience, was measured (Rammstedt et al., 2013).

Finally, a task mimicking a ticket vending machine was adopted from a previous study (Sengpiel, 2016). Here, a task sheet containing four different ticket types with different difficulty levels (1x easy, 2x middle, 1x difficult) was handed out to the participants. For instance, the participant was instructed to select two group tickets for a specific fare zone (e.g., Berlin ABC) within the user interface of the ticket vending machine. There was no time restriction and only correctly selected tickets received one point. In total, four points could be achieved.

Parallel test versions were administered in a counterbalanced order for the LPS 50+, MWT, VLMT and the ticket vending machine.

In total, eleven participants had to be excluded from the respective analysis. Six were excluded since their behavioral performance was more than 3 SD above the group's mean at t1 or t2. More precisely, for VLMT recognition: one participant (CON group); for digit span forward: one participant (CON group); for TMT-A: one participant (FAM group); and for TMT-B: three participants (one NOV group and two CON group). Moreover, one participant (NOV group) did not complete the VLMT recognition and, therefore, was also excluded. Finally, four participants had to be excluded for technical reasons from the analysis of the ticket vending machine data (one participant FAM and three participants CON group). **Table 4.1** shows the number of subjects included in the analyses for each task and group.

Table 4.1. Number of subjects included in the analysis of each test.

Analysis	Number of participants (total)	Number of participants (NOV)	Number of participants (FAM)	Number of participants (CON)
LPS 50+	83	28	28	27
MWT	83	28	28	27
VLMT learning	83	28	28	27
VLMT recall	83	28	28	27
VLMT consolidation	83	28	28	27
VLMT recognition	81	27	28	26
d2-R BZO	83	28	28	27
d2-R KL	83	28	28	27
Digit span forward	82	28	28	26
Digit span backward	83	28	28	27
TMT-A	82	28	27	27
TMT-B	80	27	28	25
Ticket vending machine	79	28	27	24

4.2.4 Cognitive training

The cognitive training comprised a total of 12 training sessions over four weeks. Participants were instructed to perform three training sessions each week, ideally with one day between each session. The tablets were programmed in a manner that it was not possible to perform more than one training a day or more than three trainings per week. If the participants tried to perform an additional training, a specific note was displayed. Moreover, the tablet contained a calendar app with highlighted days of already finished trainings, to help the participants to keep an overview of the training intervals. In most cases, participants were tested at t2 within the consecutive week of the last training session (see results).

A typical 2-back working memory task was used in this study. Digits were subsequently displayed on the tablet (for 500 ms, followed by a fixation cross for 1500 ms) and subjects had to identify those digits that were identical to the one shown two items before. Responses were given by button presses on the tablet. Each training session consisted of nine runs, 4 min each.

In these 4 min, 50 s periods of the 2-back task were followed by 10 s long silent nature movies (no overt task required except watching, see below). After each run (i.e., four 2-backs plus movies), an interval scale appeared on the tablet prompting participants to rate the previously presented four movies (range from very uninteresting to very interesting). After the rating, the task could be continued by pressing a button (**Figure 4.3**). After approx. 36 min (short breaks after the rating scale excluded), the session was completed.

Both experimental groups (NOV and FAM) only differed in the presented movie types. While the NOV group watched, in total, 432 novel (i.e., unique) movies (36 per session), the FAM group watched the same five repeating movie clips over all 12 training sessions (also 432 times in total). In other words, the movies in the FAM group were initially novel but quickly became familiar within the first training session.

The movies depicted nature scenes from different continents (i.e., Africa, America, Asia, Europe, Oceania), each further divided into different regions. For the NOV group, the 432 movie clips were well balanced and randomized across the different locations. No humans were shown during the sequences and emotional content was avoided (e.g., hunting predators). In both groups, participants were instructed to carefully watch the movies (no other task was required). To further ensure that participants payed attention to the movies (especially in the FAM group), they were only 10 s long and randomly presented.

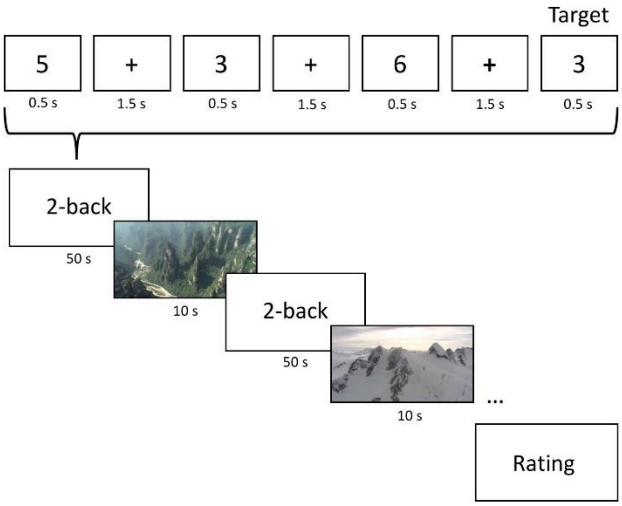

Figure 4.3. Cognitive training task. In the 2-back task, subjects had to identify those digits that were identical to the one shown two items before. The 2-back task was intermixed with video sequences. The NOV group watched novel movie sequences, while the FAM group watched five repeating movies during the whole training period.

4.2.5 Image acquisition

Structural MRI was performed at the University of Lübeck using a 3T Siemens Magnetom Skyra scanner equipped with a 64-channel head coil. Whole-brain MPM (scanning time approx. 20 min) was acquired as reported previously (Weiskopf and Helms, 2008; Weiskopf et al., 2013) using multi-echo 3D FLASH at 1 mm isotropic resolution. The volumes (voxel size 1 x 1 x 1 mm, matrix 176 x 256) were acquired for T1, PD, and MT weightings. The weightings differed in TE, TR, and flip angles. T1-weighted: six echo times (TE = 2.2, 4.7, 7.2, 9.7, 12.2, 15 ms), TR = 19 ms and flip angle = 20°; PD-weighted: eight echo times (TE = 2.2, 4.7, 7.2, 9.7, 12.2, 15, 17.5, 20 ms), TR = 24 ms, flip angle = 6°; MT-weighted: six echo times (TE: 2.2, 4.7, 7.2, 9.7, 12.2, 15 ms), TR = 37 ms, flip angle = 6°. A Gaussian MT-pulse following Siemens product sequences was used. To shorten the scan duration, GRAPPA with an acceleration factor 2 and partial Fourier acquisition 6/8 were applied. Subsequently, two runs of DWI using an EPI sequence were performed during the same scanning session (scanning time approx. 16 min). The images were later used for further analysis (results will be reported elsewhere).

MR data were further processed using the Statistical Parameter Mapping framework (SPM 12, Wellcome Trust Center for Neuroimaging, London) and MATLAB software (R2014b version, Mathworks). R2* maps were calculated through a regression of the log signal from the PD-weighted echoes. Averaging the set of echoes for each weighting increased the signal-to-noise-ratio for estimation of the MT map (Helms and Dechent, 2009). The semiquantitative MT map was calculated as described by Helms et al. (Helms et al., 2008a, 2008b). Subsequently, images were slightly manually re-orientated using SPM Check Reg and Display options (Ashburner, 2015).

4.2.6 Voxel-based morphometry and voxel-based quantification

GM volumes were processed and analyzed following a protocol for VBM using SPM's batch system (Ashburner and Friston, 2000; Ashburner, 2015). Since MT maps provide increased contrast for subcortical regions (Helms et al., 2009; Lorio et al., 2014), in a first step, they were used for segmentation of the different tissue groups. Subsequently, images of GM, WM, and CSF were generated in native space (Ashburner and Friston, 2005). Applying high dimensional warping, images were then normalized to MNI space using the DARTEL algorithm implemented

in SPM, scaled by the Jacobian determinants of the deformation field and smoothed with an isotropic Gaussian Kernel of 6 mm FWHM. Finally, the resulting smoothed, modulated and normalized images were used for statistical analysis.

VBQ analysis provides sensitivity to tissue microstructure and is therefore well suited to test differences in R2* and MT, which are sensible marker for alterations in subcortical brain regions. VBQ was processed using the open source hMRI toolbox (Tabelow et al., 2019) embedded in the SPM framework. The toolbox combines both the VBQ (Draganski et al., 2011) and the MPM (Helms et al., 2008b, 2009; Weiskopf et al., 2011, 2013) approach. Using the integrated processing pipeline of the toolbox, the previously generated MT maps were further processed using the modules tissue segmentation (GM, WM, and CSF), DARTEL, creation of templates, and normalization to MNI space. Subsequently, tissue-weighted smoothing with a FWHM isotropic Gaussian kernel of 3 mm (Draganski et al., 2011) was performed. Resulting images of R2* and MT (each separately in GM and WM subspace) were used to indirectly test for differences in iron levels (R2*) and myelination (MT) of brain tissue (see also Draganski et al., 2011; Callaghan et al., 2014).

4.2.7 Statistical analysis

For both experimental groups, corrected hit rates (cHRs) of the 2-back training task were calculated (range -1 to 1, while 1 means perfect discrimination between targets and no targets). The cHRs of correctly identified 2-back trials were defined as follows:

$$\text{cHR} = \frac{hits}{possible\ correct\ hits} - \frac{false\ alarms}{possible\ false\ alarms}.$$

The reaction times (RTs) for hits within each training session were averaged for subsequent between-subject analyses. RTs of 2 SD above and below the subject's mean were excluded. Further, participants with more than 3 SD above the overall mean of a specific neuropsychological test were excluded from the respective analysis.

To test for possible group differences at the beginning of the training, a t-test for independent samples with the between-subject factor group (NOV, FAM) was conducted on cHRs and RTs, respectively, from the first training session. The effects of the training and novelty

on cHR and RT, respectively, were analyzed using a two-way mixed-design ANOVA (2x2) with the between-subject factor group (NOV, FAM) and the within-subject factor time (start, end). Transfer effects to other cognitive domains and possible effects of novelty were investigated using separate two-way mixed-design ANOVAs (3x2) for repeated measurements with the between-subject factor group (NOV, FAM, CON) and the within-subject factor time (t1, t2).

The relationship of group and movie rating was calculated using a t-test for independent samples with the between-subject factor group (NOV vs. FAM). Further, correlation analyses were performed to investigate possible relationships between (a) training gains (cHR start/end differences) and MoCA scores, (b) training gains and personality traits (i.e., extraversion, agreeableness, conscientiousness, neuroticism, openness to experience), (c) transfer effects and MoCA scores and (d) transfer effects and personality traits.

Finally, post-hoc t-tests were used when applicable and Bonferroni corrected with an adjusted alpha level of 0.016 (0.5/3 – comparison between the three groups). Similarly, correlation analyses were adjusted for the number of comparisons (see results). All behavioral analyses were performed using IBM SPSS Version 24.

Possible structural brain changes between pre- and post-test were analyzed with SPM12 using MATLAB 2014b. Main effects of the factor group and time were calculated using a full factorial design. A flexible factorial design - well suited for models with repeated measurements - was conducted for analyses of interaction effects between group and time. The model comprised three factors (factor 1: subject, factor 2: group [three levels: NOV, FAM and CON], factor 3: time [two levels: t1 and t2]). Contrasts were defined as described by Gläscher and Gitelman (2008). To further investigate possible training effects on the structural integrity of the basal ganglia, a mask containing the putamen, caudate, pallidum, and NAcc was applied. The mask was taken from the Harvard-Oxford-Atlas (50% probability mask), implemented in the FMRIB Software Library (FSL; Jenkinson et al., 2012).

A multiple regression analysis was conducted including all three groups in order to test for relationships between baseline structural integrity and possible transfer effects. For this, pre/post differences of each neuropsychological test were correlated with baseline MRI images (i.e., VBM and VBQ). For both experimental groups (NOV + FAM), a second multiple regression

analysis was calculated. Here, baseline MRI and training gains (cHR start/end differences) were correlated.

Since there were no significant training effects for TMT-A or TMT-B and in order to reduce the number of comparisons, for the structural analyses, scores of digit span forward and backward and scores of TMT-A and TMT-B were combined (i.e., times were added). Due to two outliers (> 3 SD) in the combined TMT, separate linear regression analyses of VBM and VBQ were conducted.

Data were normally distributed for most groups and time points, except for a few cases. For instance, normality assumption was violated at t2 for the digit span forward data in the FAM group. Moreover, homogeneity of variance was given, except for data from the ticket vending machine. Since there are no suitable non-parametrical tests for mixed design ANOVAs and given the rather large sample size, no additional analyses were conducted. However, regarding the movie ratings, the non-parametric Mann-Whitney U test was calculated. For the regression analyses, including the BFI-10, Kendall's tau non-parametric correlation coefficient was used.

4.3 Results

4.3.1 Behavioral data

In total, most participants completed all training sessions as instructed (NOV group mean: 11.79 ± 0.50 sessions; FAM group mean: 11.61 ± 0.88 sessions). More precisely, in the NOV group, 12 sessions were completed by 23 participants, 11 sessions were completed by 4 participants, and 10 sessions were completed by 1 participant. In the FAM group, 12 sessions were completed by 21 participants, 11 sessions were completed by 5 participants, 10 sessions were completed by 1 participant, and 8 sessions were completed by 1 participant. Two t-tests for independent samples on cHRs and RTs, respectively, for the first training session did not reveal significant effects for cHRs or RTs (cHR: $t[53] = 0.0456$, $p = 0.964$, Cohen's $d = 0.0123$; RTs: $t[53] = 0.766$, $p = 0.447$, Cohen's $d = 0.207$) indicating no statistically significant differences between groups at baseline.

A 2x2 ANOVA on cHR with the between-subject factor group (NOV, FAM) and the within-subject factor time (start, end) revealed a main effect of time (cHR: $F[1,53] = 227.293$, p

< 0.001, partial η^2 = 0.811). Post hoc comparison revealed higher cHR at the end of the training as compared to the beginning (cHR start mean: 0.64; cHR end mean: 0.88; **Figure 4.4A**). However, there was no main effect of group (F[1,53] = 0.027, p = 0.871, partial η^2 = 0.001) and no significant group by time interaction (cHR: F[1,53] =0.052, p = 0.820, partial η^2 = 0.001). A similar pattern emerged in the 2x2 ANOVA on RT: there was a main effect of time (F[1,53] = 51.830, p < 0.001, partial η^2 = 0.494), which was driven by faster RTs for the end as compared to the beginning of the training (RT start mean: 933.05 ms; RT end mean: 831.43, **Figure 4.4B**). However, there was no main effect of group (F[1,53] = 1.983, p = 0.165, partial η^2 = 0.036) and no group by time interaction (RT: F[1,53] = 1.736, p = 0.193, partial η^2 = 0.032).

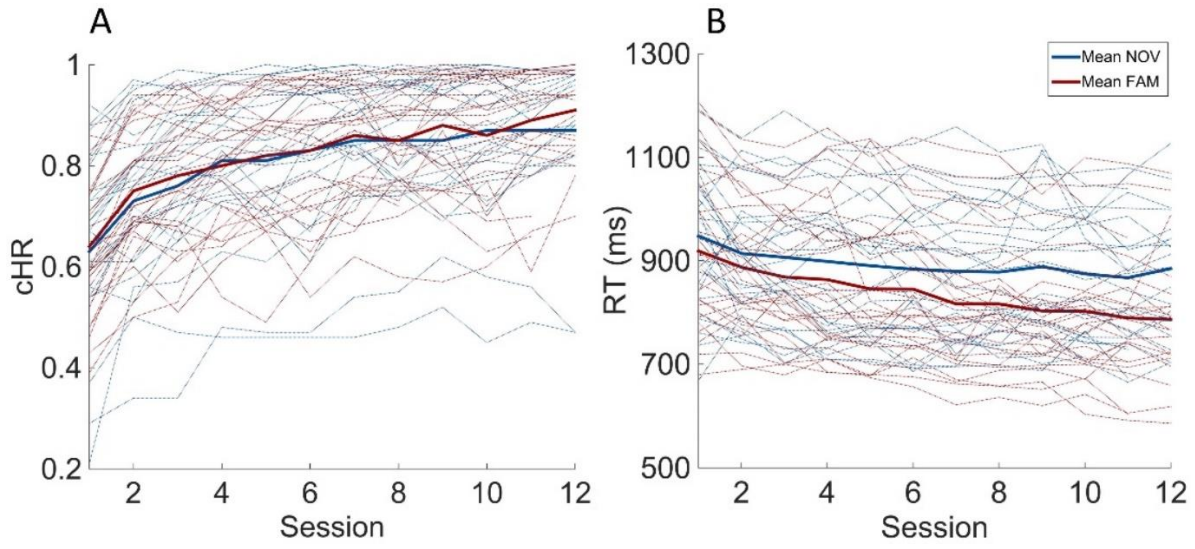

Figure 4.4. Training performance over time. Graphs show an increase of corrected hitrate (cHR; **A**) and a decrease of reaction time (RT; **B**) for both experimental groups over time. Thicker lines represent mean values of the respective group, thinner lines represent individual performances. Note, that not all participants completed the 12 training sessions (NOV: 22 = 12 sessions, 4 = 11 sessions, 1 = 10 sessions; FAM: 21 = 12 sessions, 5 = 11 sessions, 1 = 10 sessions, 1 = 8 sessions).

For the NOV group, the average number of days between t1 and t2 assessment was 31.5 ± 4.38, for the FAM group 31.2 ± 4.17, and for the CON group (which did not participate in a training program) 30.8 ± 4.78 days. The average number of days between the last session of the training and t2 was 3 ± 1.78 days for the NOV group and 3.11 ± 1.37 days for the FAM group. Due to technical issues, the last analysis includes only data from 37 participants (NOV n = 18, FAM n = 19).

Separate 3x2 ANOVAs with the factors group (NOV, FAM, CON) and time (t1, t2) revealed main effects of *time* for Gf *(LPS 50+)*, verbal memory *(VLMT learning, free recall and recognition)*, processing speed *(d2-R working speed and concentration)*, and executive function *(TMT-A and TMT-B)* (see **Table 4.2** for statistical values). Post hoc t-tests revealed higher scores for all these tests after training as compared to before training (all p's < 0.008), indicating performance improvements over time (**Table 4.2**).

No main effects of *time* were found for Gc (*MWT*), a subtest of the verbal memory task (*VLMT consolidation*), numeric memory (*digit span forward* and *backward*), and the *ticket vending machine* (**Table 4.2**). There were no main effects of group for any score (**Table 4.2**).

Interactions (*time*group*) could be revealed for processing speed (*d2-R working speed, BZO:* $F[2,80] = 3.588$, $p = 0.032$, partial $\eta^2 = 0.082$), and verbal memory (*VLMT learning:* $F[2,80] = 3.254$, $p = 0.044$, partial $\eta^2 = 0.075$). There were no other interactions (**Table 4.2**).

Post hoc analysis (paired sample t-tests) revealed a significant difference for the pre vs. post comparison in *d2-R working speed* (BZO) in the NOV and FAM group (NOV: $p < 0.001$, FAM: $p < 0.001$) but not the CON group ($p = 0.074$). For the verbal memory interaction (*VLMT learning*), a significant difference for the pre vs. post comparison could be revealed for all three groups (NOV: $p=0.008$, FAM: $p < 0.001$, CON: $p=0.006$); see **Figure 4.5**), but the comparison of the differences between groups did not survive Bonferroni correction ($p > 0.016$). That means, despite a significant time*group interaction ($p=0.04$), post hoc tests could not pinpoint significant differences between groups for VLMT learning.

Table 4.2. Results and statistical values of the 2x3 ANOVAs. For each neuropsychological test, a 2x3 ANOVA with the factors time (t1, t2) and group (NOV, FAM, CON) was calculated. Significant p-values are highlighted in bold letters.

		Main effects time		
Domain	*Test*	*F statistic*	*P value*	*Effect size partial η²*
Fluid intelligence	LPS 50+	F[1,80] = 76.18	**< 0.001**	0.488
Crystallized intelligence	MWT	F[1,80] = 0.791	0.376	0.010
Verbal memory	VLMT learning	F[1,80] = 49.756	**< 0.001**	0.383
	VLMT free recall	F[1,80] = 21.323	**< 0.001**	0.210
	VLMT consolidation	F[1,80] = 1.476	0.228	0.018
	VLMT recognition	F[1,78] = 19.203	**< 0.001**	0.198
Processing speed	d2-R working speed (BZO)	F[1,80] = 48.259	**< 0.001**	0.376
	d2-R concentration (KL)	F[1,80] = 53.775	**< 0.001**	0.402
Executive functioning	TMT-A	F[1,79] = 6.976	**0.01**	0.081
	TMT-B	F[1,77] = 6.099	**0.016**	0.073
Numeric memory	Digit span forward	F[1,79] = 0.692	0.408	0.009
	Digit span backward	F[1,80] = 1.998	0.161	0.024
Everyday ability	Ticket vending machine	F[1,76] = 2.106	0.151	0.027
		Main effects group		
Fluid intelligence	LPS 50+	F[2,80] = 0.575	0.565	0.014
Crystallized intelligence	MWT	F[2,80] = 0.509	0.603	0.013
Verbal memory	VLMT learning	F[2,80] = 1.134	0.327	0.028
	VLMT recall	F[2,80] = 1.122	0.331	0.027
	VLMT consolidation	F[2,80] = 0.267	0.767	0.007
	VLMT recognition	F[2,78] = 0.587	0.558	0.015
Processing speed	d2-R working speed (BZO)	F[2,80] = 1.303	0.278	0.032
	d2-R concentration (KL)	F[2,80] = 0.816	0.446	0.020
Executive functioning	TMT-A	F[2,79] = 0.169	0.845	0.004
	TMT-B	F[2,77] = 0.496	0.611	0.013
Numeric memory	Digit span forward	F[2,79] = 1.531	0.223	0.037
	Digit span backward	F[2,80] = 0.606	0.548	0.015
Everyday ability	Ticket vending machine	F[2,76] = 0.045	0.956	0.001
		Interactions (time*group)		
Fluid intelligence	LPS 50+	F[2,80] = 1.061	0.351	0.026
Crystallized intelligence	MWT	F[2,80] = 0.097	0.907	0.002
Verbal memory	VLMT learning	F[2,80] = 3.254	**0.044**	0.075
	VLMT recall	F[2,80] = 2.880	0.062	0.067
	VLMT consolidation	F[2,80] = 1.310	0.276	0.032
	VLMT recognition	F[2,78] = 1.026	0.363	0.026
Processing speed	d2-R working speed (BZO)	F[2,80] = 3.588	**0.032**	0.082
	d2-R concentration (KL)	F[2,80] = 2.590	0.081	0.061
Executive functioning	TMT-A	F[2,79] = 0.844	0.434	0.021
	TMT-B	F[2,77] = 0.966	0.385	0.024
Numeric memory	Digit span forward	F[2,79] = 1.345	0.267	0.033
	Digit span backward	F[2,80] = 0.911	0.406	0.022
Everyday ability	Ticket vending machine	F[2,76] = 0.110	0.896	0.003

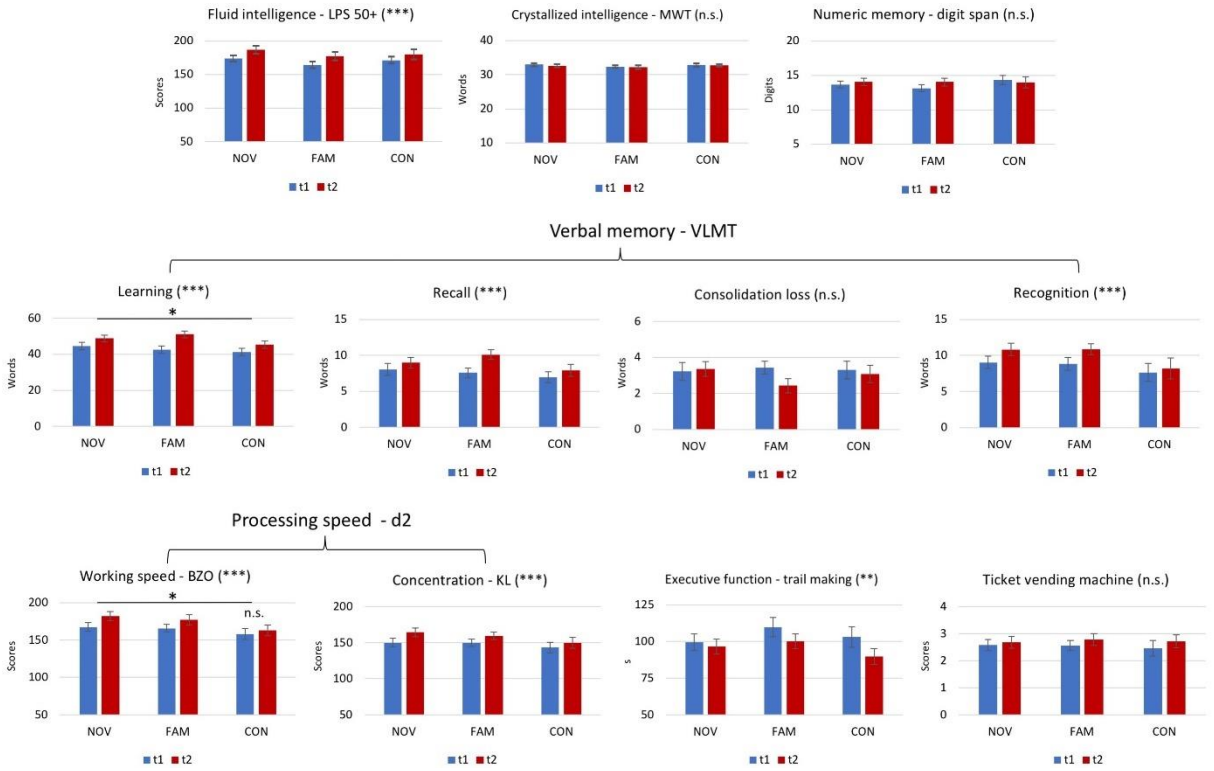

Figure 4.5. Results of the neuropsychological assessment. Significant main effects of time (t1 vs. t2) are marked in brackets (* = p<0.05; ** = p<0.01; *** = p<0.001; n.s. = not significant). For displaying purposes, values of digit span forward and backward (= numeric memory) as well as TMT-A and TMT-B (= executive function) were combined. A significant interaction of group and time was only observed for working speed (BZO) and VLMT learning (see text), which are marked with an asterisk.

A non-parametrical equivalent for a t-test for independent samples (i.e., Mann-Whitney U test) on movie ratings revealed a main effect *group* (U = 196, p = 0.002, Cohen's d = 0.821). Post-hoc analysis showed that novel movies were rated more positively as compared to familiar movies (**Figure 4.6**).

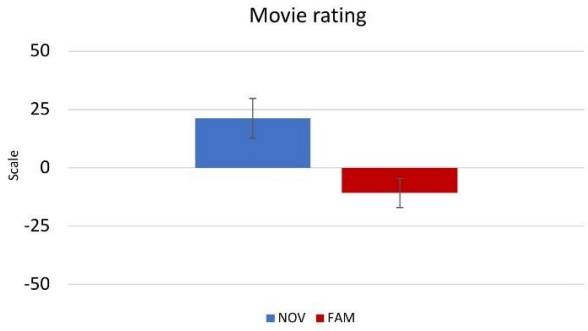

Figure 4.6. Main effect of movie rating. Participants of the NOV group rated movie sequences, which were presented during the training session, more positively (mean 21.22) than participants of the FAM group (mean -10.75).

Finally, exploratory correlation analyses (first the NOV and FAM group separately, followed by across groups) of behavioral training gains (cHR start/end differences) and MoCA scores, did not reveal any significant effects. Similarly, there was no significant correlation between training gains and personality traits (all p's > 0.05).

Similarly, correlation analyses for pre vs. post training difference of the cognitive tests and MoCA scores, and pre vs. post training difference of the cognitive tests and personality traits also did not reveal any significant effects (all p's ≥ 0.01, and therefore, did not survive Bonferroni corrections with adjusted alpha levels of 0.05/13 and 0.05/65, respectively).

4.3.2 Structural data

In a first full-factorial design with the factors group (NOV, FAM) and time point (pre, post training), no main effects were found for group or time (FWE, $p < 0.05$ whole brain) for measures of GM volume (VBM), myelination (VBQ on MT maps) and iron levels (VBQ on R2* maps). Subsequently, a flexible factorial design did not reveal any group by time interactions (FWE, $p < 0.05$ whole brain). To further examine possible effects of the cognitive training on subcortical brain regions, a mask for the basal ganglia was applied for VBM and VBQ (R2* and MT maps) with a more liberate threshold (FWE, $p < 0.05$ cluster level; cluster size > 50 voxel). Again, these analyses did also not reveal any significant effects.

Finally, exploratory multiple regression analyses (FWE, $p < 0.05$ whole brain) were conducted for baseline MRI data (VBM and VBQ) and pre/post differences of the cognitive assessments (including training gains). No statistically significant effects could be revealed.

4.4 Discussion

We investigated the behavioral and neural effects of a 4-week cognitive training and their potential modulation by novelty. As expected, the training improved performance in the 2-back working memory task but these effects did not transfer to other untrained domains. Although novel movies were rated as more positive than repeated ones, novelty did not drive performance in the trained or in any untrained task. At the neural level, no pre vs. post training differences could be observed in any micro- and macrostructural modality (R2*, MT and GM). Together, our findings suggest that, in healthy older adults, the benefits of a 4-week working

memory training do not transfer to other untrained abilities, and a combined passive exposure to novelty has no further promoting effects. In the following, we will discuss possible explanations of our findings and conclude that, in the light of our study, the effects of cognitive training appear rather weak.

Several studies have demonstrated beneficial effects of cognitive training to untrained abilities (Jaeggi et al., 2008; Heinzel et al., 2016; Salminen et al., 2016). However, more recent work casts doubts about the success with regard to transfer effects (Owen et al., 2010; Rabipour and Raz, 2012; Redick et al., 2013; Simons et al., 2016; Bellander et al., 2017). Here, we can show that benefits of a 4-week cognitive training (2-back task) are evident in the trained task (**Figure 4.4**), which agrees with most training studies, but they do not transfer to other near (i.e., working memory) or far (i.e., verbal memory) cognitive domains. At least a near transfer effect would have been plausible given the notion that brain plasticity is restricted to the trained task (Lindenberger et al., 2017) and transfer to other domains is only possible if commonalities to the training task exist (Lövdén et al., 2010). Therefore, it remains unclear under which conditions transfer effects (near and far) may occur.

In agreement with the notion of a transfer effect, Heinzel et al. (2016) could show that a similar version of a working memory training improves processing speed, fluid intelligence, and executive functions. While BZO (working speed in the d2-R-test) also improved by training in our study, it does not consider false positives and omissions. Therefore, KL appears to be a more suitable measure of concentration in the d2-R-test, which however, in our study did not benefit from training (**Figure 4.5**). Another critical difference to Heinzel et al. (2016) is that we did not tailor the training adaptively to the participants' performance level. While individualized trainings appear to be a critical factor for training success and transfers effects (Buitenweg et al., 2012), we aimed to avoid differences between groups with regard to training demands. In other words, we expected novelty to drive training success (see below for an explanation), which, in case of individual adaptations, could have resulted, for instance, in faster digit presentations or longer delays (depending on how an adaptation is realized) between the novelty and familiarity group. This was avoided by a constant training paradigm for all

participants. Future studies may take this aspect into account more rigorously, especially in order to avoid ceiling effects (**Figure 4.4**).

Another explanation for no transfer effects in our study may relate to task complexity. For instance, Jaeggi et al. (2008), who could demonstrate transfer effects in older adults on Gf, have used a working memory training task that required both visual and auditory modalities, and therefore, relied much more on binding processes and attentional control. Similarly, playing a video game for one month (three times per week) only led to transfer effects in a working memory task when it required multitasking but not in a simpler single version (Anguera et al., 2013). Interestingly, these training effects persisted for six months and were associated with functional changes in midline frontal theta (4-7 Hz) power and long-range theta coherence as measured with EEG.

The absence of transfer effects may also relate to training duration and sample size. However, several previous studies - showing training gains and transfer effects - included fewer subjects and have the same number of sessions as our study (Anguera et al., 2013; Heinzel et al., 2014, 2016). Furthermore, expected transfer effects do not necessarily need to be small. Instead, in Heinzel et al. (2016) transfer effects after a 4-week cognitive training were rather strong (partial $\eta^2 > 0.14$, as defined in Cohen, 1988). Specifically, the working memory training in their study had transfer effects on performance in a test on processing speed (d2) with a partial η^2 of 0.28, a test on executive functions (Stroop test) with a partial η^2 of 0.19, and a test on fluid intelligence (LPS) with a partial η^2 of 0.14. Moreover, based on their findings, a power analysis (G*Power) shows that our study involved a sufficient number of subjects in order to replicate their findings with a power of at least 80% (i.e., processing speed (d2): 13 per group, executive functions (Stroop): 19 per group, Gf (LPS): 27 per group). Therefore, insufficient power or training sessions do not explain why transfer effects could not be revealed in our study. In any case, including a sufficient number of subjects is important for any future study addressing training and transfer effects.

In accordance with no transfer effects, but against our hypothesis, a thorough examination of GM volume, MT and R2* in both a whole brain and a more sensitive region of interest analysis could not reveal differences between pre- and post-training MRI data. One of

the most striking and earliest findings in favor of a link between practice and structural brain plasticity is provided by Draganski et al. (2004), who could show that a three months juggling training in younger adults led to GM changes within the mid-temporal area and posterior intraparietal sulcus. Importantly, these behavioral and structural effects were transient since fluent juggling abilities and increases of GM volume returned to baseline three months after the training ended (see Boyke et al., 2008 for a replication in older adults). More recently, volume changes within the human motor cortex were described over the time course of seven weeks (Wenger et al., 2017). Specifically, right-handed human subjects practiced in non-dominant, left-hand writing and drawing, while up to 18 structural brain scans (MRI) were acquired. Importantly, increases in GM volume in the primary motor cortices were most pronounced after four weeks and they were no longer reliable after another three weeks despite still increasing task performance. Therefore, experience-dependent structural brain changes appear to progress in a non-linear fashion, which nicely fits to the 'overproduction-pruning' model, suggesting a fast increase of synapses only at the beginning of the intervention and a return to baseline over time (Lindenberger et al., 2017). With regard to our findings, more brain scans throughout the training period may have helped to identify possible non-linear structural brain changes. Although the absence of transfer effects at the end of the training may argue against it, the clear improvement over time in the training task may be associated with non-linear structural plasticity. In any case, time-series sampling at the neural (and possibly behavioral) level may be considered in future studies.

Alternatively, the improvements of our 4-week working memory training may only be associated with functional but not structural changes. For instance, based on BOLD fMRI, the study by Heinzel et al. (2016) found reduced hemodynamic activity in frontal brain regions associated with working memory processing, suggesting training-related increases in processing efficiency. While structural brain changes may need more time to occur, the above-mentioned study by Wenger et al. (2017) shows that, in principle, brain changes can be detected within four weeks. Future studies, therefore, may focus on both functional and anatomical brain changes.

Novel movie clips throughout the training did not further promote training gains or transfer effects. This assumption was based on the notion that novelty activates the

dopaminergic mesolimbic system and thereby drives plasticity, including learning and memory (Lisman and Grace, 2005; Lisman et al., 2011). In humans, for instance, novel scene images improved subsequent memory (Fenker et al., 2008), and the exploration of a novel VR, compared to a familiar VR, enhanced recall (Schomaker et al., 2014). These effects are comparable with animal studies showing that LTM is not only promoted through novelty exploration before but also after learning (Li et al., 2003; Moncada and Viola, 2007; Ballarini et al., 2009; Wang et al., 2010a). At the neural level, novelty activates the SN/VTA, striatum, and the hippocampus (Bunzeck and Düzel, 2006; Zaehle et al., 2013; Bunzeck et al., 2014; Herweg et al., 2018) providing further evidence for a link between dopaminergic neuromodulation and novelty.

Along the same lines, an impoverished environment (i.e., lack of social or physical stimuli) can lead to cognitive decline in animals and humans (see as a review Volkers and Scherder, 2011), further suggesting a positive effect of novelty. Importantly, older animals were more affected by impoverished environments than young animals (Bell et al., 2009), but, interestingly, these negative effects seemed to be reversible when resettled to an enriched environment (Winocur, 1998). In humans, complex work environments may increase intellectual abilities and this effect was even higher in older than young workers (Schooler et al., 1999). The importance of experiencing novelty at work (i.e., work-task changes) has been further underlined by a positive correlation with processing speed, working memory and GM volume in older adults (Oltmanns et al., 2017). Finally, a longitudinal study revealed that complex leisure time activities (e.g., reading books, visits of art institutions, or hobbies) increased intellectual functioning in older adults, while less complex activities led to reverse effects (Schooler and Mulatu, 2001). Together, these findings stressing the importance of stimulating and novel environments in the context of age-related plasticity.

Although our nature movies were rated as more positive compared to familiar ones there was no beneficial effect of novelty on performance in the training task or transfer effects. To further understand this issue, we already conducted an additional behavioral study (Biel and Bunzeck, 2019), in which young participants were exposed to novelty (same movies as in the present study) before, directly after, or 15 min after encoding of a word list. In line with our findings here, novel movies were rated as more positive, but they had no effect on subsequent

recognition. We concluded that a passive exposure to novelty is not sufficient in order to promote plasticity and learning. Instead, a sense of agency, for instance through active choices during novelty processing, may be required (Murty et al., 2015). Therefore, a parsimonious explanation is that a stronger sense of agency, possibly associated with the engagement of memory related brain regions, is necessary in order to induce a positive effect of novelty on training gains and transfer effects.

After the training, task performance was significantly enhanced for most tests in both the novelty and familiarity group. However, such pre vs. post differences were also significant in the passive control group after four weeks of no training, excluding the possibility of a specific training-related transfer effect (**Figure 4.5**). Therefore, a more likely explanation relates to retesting, which has previously been described (Scharfen et al., 2018). Specifically, repeated administration of a cognitive ability test can lead to an improvement of a third of a standard deviation, which may relate to practice rather than the measured ability itself (Lievens et al., 2007). Further, changes in confounding factors like anxiety and test familiarity at the second appointment can influence better test results (Reeve et al., 2009). Together, observing similar pre vs. post differences in our intervention groups and the passive control group can best be explained by retest effects. From a more general perspective, this highlights the importance of a passive control group in cognitive training studies in order to correctly assess training benefits.

The importance of inter-individual differences in training studies has previously been highlighted (e.g., Buitenweg et al., 2012). Specifically, Jaeggi et al. (2014) suggested that the effects of a working memory training may depend on factors including motivation, need for cognition, preexisting abilities and implicit theories about intelligence. Further, in another study with young participants, the success of a 6-week juggling training (i.e., learning slopes) correlated with GM volumes within medial occipito-parietal brain regions at baseline (Sampaio-Baptista et al., 2014). Therefore, we investigated the relationship between training effects (gains and transfer, respectively) and cognitive abilities (MoCA), training effects, and personality traits (Big-Five), as well as training effects and baseline structural integrity. None of these correlations, which were collapsed across the experimental groups and therefore included

more than 50 subjects, revealed statistically significant effects. These analyses may not include all possible factors mentioned above, but they suggest that a relationship between individual differences and training gains may be more complex than previously thought.

Finally, a potential limitation of many training studies relates to the abstract nature of assessing cognitive functioning in older adults via standardized tests in a laboratory environment. Although standardized tests are indispensable, measuring everyday functioning in older adults and importantly, possible effects of cognitive training on those, can be challenging. In order to address this issue, we implemented a ticket vending machine, mimicking everyday functioning. However, as stated above, no improvements could be revealed. Therefore, future training studies should target a wider battery of everyday functioning in a non-laboratory environment (i.e., questionnaires addressing daily life abilities).

Together, in healthy older adults a 4-week 2-back working memory training improved working memory abilities. However, these training gains were restricted to the trained task and did not transfer to other cognitive domains. Novelty presentation throughout the training, supposed to be associated with dopaminergic neuromodulation, did not further promote training gains or transfer effects. At the neural level, pre vs. post training comparisons did not reveal any structural brain changes in GM, myelin, or iron levels. Therefore, our findings are in line with several recent studies, indicating that brain plasticity is specific to the trained ability and associated structural brain changes may be non-linear.

5 Study 3: Novelty before or after word learning does not affect subsequent memory performance

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Abstract

In humans, exposure to novel images and exploration of novel virtual environments before the encoding of words improved subsequent memory performance. Animal studies revealed similar effects of novelty, both before and after learning, and could show that hippocampus-dependent dopaminergic neuromodulation plays an important role. Here, we further investigated the effects of novelty on LTM in humans using a novel paradigm employing short sequences of nature movies presented either before or at two time points after learning of unrelated words. Since novelty processing is associated with a release of DA into the hippocampus, we hypothesized that novelty exposure primarily affects hippocampus-dependent memory (i.e., recollection) but not hippocampus-independent memory (i.e., familiarity). We tested 182 healthy human subjects in three experiments including a word-learning task followed by a 1-day delayed recognition task. Importantly, participants were exposed to novel (NOV) or familiar movies (FAM) at three time points: (experiment 1) directly after encoding of the word list, (experiment 2) 15 min after encoding, (experiment 3) 15 min prior to encoding. As expected, novel movies were perceived as more interesting and led to better mood. During word recognition, RTs were faster for remember as compared to familiarity responses in all three experiments, but this effect was not modulated by novelty. In contrast to our main hypothesis, there was no effect of novelty – before or after encoding – on subsequent word recognition, including recollection and familiarity scores. Therefore, an exposure to novel movies without an active task does not affect hippocampus-dependent and hippocampus-independent long-term recognition memory for words in humans.

5.1 Introduction

A few recent studies in humans have shown that the exposure to novelty before a learning phase improves subsequent memory (Fenker et al., 2008; Ballarini et al., 2013; Schomaker et al., 2014). For instance, the presentation of novel images before a word-learning task enhanced free recall and recollection-based memory (Fenker et al., 2008); recall rates of words could be enhanced through an active exploration of a novel virtual environment before the learning phase (Schomaker et al., 2014); and already familiar scene images were subsequently better recognized when they were presented in the context of novel images as compared to a context with very familiar images (Bunzeck and Düzel, 2006). These observations in humans largely fit to animal studies, which also show that LTM is not only promoted through novelty exploration before – but also after – learning (Moncada and Viola, 2007; Wang et al., 2010a). To our knowledge, however, such a positive effect of novelty after learning has not been reported in humans yet.

The processing of novel information recruits the dopaminergic mesolimbic system. Specifically, the hippocampal-VTA loop model suggests that the medial temporal lobe (including the hippocampus and surrounding cortex) detects novelty by comparing incoming with predicted information (Lisman and Grace, 2005; Lisman et al., 2011). The resulting neural novelty signal is then sent to the DA neurons in the SN/VTA via a polysynaptic path, including the subiculum, NAcc, and ventral pallidum. In turn, DA neurons back-project to the hippocampus, where DA is involved in several forms of learning. For instance, the late phase of hippocampal LTP is DA dependent (O'Carroll and Morris, 2004; Granado et al., 2008), and injections of DA agonists into the hippocampus improve memory processes in rats (Packard and White, 1991). The role of the SN/VTA, hippocampus and also DA in novelty processing has been underlined in functional imaging studies in humans (Chowdhury et al., 2012; Bunzeck et al., 2014), and therefore, the hippocampal-VTA model helps to explain the beneficial effects of novelty on LTM. More direct evidence comes from Wang et al. who could show in rats that novelty exploration after spatial encoding improves long-term place-memory (i.e., at a behavioral level), and this effect was blocked by D1/D5 receptor antagonists (Wang et al., 2010a).

Recent studies have shown that novelty also activates the noradrenergic system, which co-releases noradrenaline and DA into the hippocampus. Therefore, hippocampal DA has two sources (McNamara and Dupret, 2017; Duszkiewicz et al., 2019), and novelty-dependent activation of the noradrenergic locus coeruleus also drives hippocampus-dependent learning (Kempadoo et al., 2016) and consolidation of everyday memory (Takeuchi et al., 2016) via dopaminergic neuromodulation.

Recognition memory in humans is often investigated using the remember/know paradigm (Tulving, 1985). It assumes that recognition can be associated with specific details or associations of the encoding episode (i.e., recollection), or in the absence of such recollective experience (i.e., familiarity). Further support for such a dual process (Yonelinas et al., 1996, 2010) comes from functional imaging studies, suggesting that different regions of the medial temporal lobe are involved in recognition memory processes depending on task demands and type of information (Diana et al., 2007). In particular, while the hippocampus and posterior parahippocampal gyrus are closely associated with recollection, the anterior parahippocampal gyrus is more associated with familiarity (Diana et al., 2007). Therefore, the hippocampus appears to be more critical for recollection but not for familiarity (Yonelinas et al., 2010). Furthermore, RTs for items that are associated with recollection are typically faster as compared to familiarity, which further indicates different processes (Dewhurst et al., 2006; Rotello and Zeng, 2008; Gimbel and Brewer, 2011). Together, the remember/know paradigm provides a good tool to differentiate hippocampus-dependent from hippocampus-independent memory performance.

In animal studies, the effects of novelty on learning are typically investigated by using an active exploration of a new vs. familiar environment (Li et al., 2003; Davis et al., 2004; Moncada and Viola, 2007; Wang et al., 2010a). Studies in humans, however, often used static images (Fenker et al., 2008) or virtual environments (Schomaker et al., 2014) before a word-learning task or static images in the context of learning (Bunzeck and Düzel, 2006). In the case of Schomaker et al. (2014) and Fenker et al. (2008), the novelty presentation was 5 min long, which was based on prior observations in animals suggesting that a 5 min novelty exploration is sufficient to facilitate LTP (Li et al., 2003); in the case of Bunzeck and Düzel (2006), however, several repeating learning contexts with novel and familiar items were approx. 6 min long,

suggesting that a limitation of 5 min might not necessarily be justified. Indeed, in a study with rats, the animals stayed in the novel environment for about 15 min, which led to a reinforcement of early- to late-LTP (Straube et al., 2003). And, finally, LTM in school children could be promoted by a 20-min novel science lesson 1 h before or after story reading (Ballarini et al., 2013). This latter finding also demonstrates that the beneficial effects of novelty have practical implications, and therefore, a thorough understanding of the underlying processes is important.

In this study, we investigated (1) whether other forms of novelty stimulation drive word-learning and (2) whether a critical time-window exists in humans (as seen in animal studies). Therefore, we employed a novel paradigm including the presentation of short (13 min) nature movies (1) shortly after, (2) 15 min after, and (3) before encoding of a word list, and tested LTM for these unrelated words after a 1-day delay (based on the assumption that DA affects late LTP and therefore LTM; Wittmann et al., 2007; Lisman et al., 2011). We expected a positive effect of novelty before and after word-learning that is particularly pronounced for hippocampus-dependent recollection. Moreover, we expected faster RTs for recollection as compared to familiarity, which might be further modulated by novelty (i.e., even faster recollection when a word was learned before or after novelty presentation). Finally, we expected novel movies to be more interesting than repeatedly presented familiar ones and a positive effect of novel movies on mental states (i.e., the novel movies lead to higher attentional states, including wakefulness, compared to familiar movies). The latter hypotheses are based on previous studies, showing high novelty preferences in particular for natural scenes as compared to faces or geometric figures (Park et al., 2010).

5.2 Materials and methods

5.2.1 Participants

In total, 192 healthy, right-handed, German-speaking participants were recruited for three experiments. Five participants were excluded because their behavioral performance (including hit rates and RTs) was more than 3 SD above the mean, one subject did not return on day 2, and four were excluded for technical reasons or other problems. Finally, 182 participants were randomly assigned into three experimental groups (NOV) and three control groups (FAM). In

experiment 1, 61 participants were tested (NOV = 32 participants, FAM = 29 participants; mean age = 23.07 ± 3.62 years, 44 women); in experiment 2, 60 participants (NOV = 31 participants, FAM = 29 participants; mean age = 22.32 ± 3.07 years, 51 women) were tested; and in experiment 3, 61 participants (NOV = 30, FAM = 31; mean age 22.69 ± 3.27 years, 51 women) were tested (**Table 5.1**). All subjects were recruited through the database of the University of Lübeck (Greiner, 2015) and signed a written informed consent. For compensation, participants received either credits points (psychology students only) or 10 € per hour (i.e., in total between 10 and 15 €). The study was approved by the local ethics committee of the University of Lübeck, Germany, and in accordance with the Declaration of Helsinki.

Table 5.1. Demographics.

	Experiment 1				Experiment 2				Experiment 3			
	Directly after encoding				15 min after encoding				15 min prior to encoding			
Groups	NOV		FAM		NOV		FAM		NOV		FAM	
n	32		29		31		29		30		31	
Age	23.31 (±3.74)		22.79 (±3.53)		23.45 (±3.49)		21.10 (±1.95)		22.83 (±3.25)		22.55 (±3.34)	
Sex	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂
n	22	10	22	7	24	7	27	2	25	5	26	5

5.2.2 Experimental design and procedure

The experiments took place on 2 consecutive days. On day 1, participants performed an encoding task in which they classified words into living vs. non-living by button presses. In total, 50 living and 50 non-living German nouns were randomly presented on a white computer screen (13 inches) in black letters (Arial, 30 point) for 1.5 s followed by a fixation point (also 1.5 s; **Figure 5.1B**). Participants were asked to respond as quickly and as accurately as possible. In case of an omission or incorrect response, a corresponding feedback appeared on the screen (i.e., "too slow" or "incorrect response"). This encoding phase took approx. 5 min.

In all three experiments, a 13-min movie phase (**Figure 5.1A**) preceded or followed the encoding task. Here, participants were instructed to carefully watch 10 s nature movie sequences (no other task was required during the movie presentation), separated by a 3 s white fixation point on a black screen.

The movies depicted different nature settings from five regions including Africa, America, Asia, Europe, and Oceania. In order to avoid a drop of attention – which could occur using only one longer movie sequence – movies were randomly presented with a duration of 10 s each. The sequences did not show any humans. In addition, scenes with strong emotional content were avoided to prevent high arousal (e.g., hunting predators). There was no relationship in terms of content between movies and words.

For the NOV groups, 60 novel sequences were presented, while the FAM groups watched three different movies, which were repeated 20 times. Since only three movies were shown to the FAM groups, a separate familiarization phase was not implemented.

For the three experiments, the novelty phase was implemented at different time points: directly after encoding (experiment 1), 15 min after encoding (experiment 2), and 15 min prior to encoding (experiment 3). During the 15-min break, participants were instructed to quietly wait on their seats. Directly after watching the movies, participants were instructed to rate the previously presented movies on an interval scale reaching from very uninteresting to very interesting. Further, shortly before and after the exposure to the movies, participants filled out a multidimensional mental state questionnaire (Mehrdimensionale Befindlichkeitsfragebogen, MDBF) covering: good mood/bad mood, wakefulness/tiredness, and calmness/restlessness.

On the second day of the experiment, participants performed a modified version of the remember/know recognition memory paradigm (Tulving, 1985). Here, the 100 words from the encoding task were intermixed with 100 new words (50 living and 50 non-living words) and randomly presented at the center of a screen. Participants were instructed to categorize these 200 words into "remember" (i.e., remembering something specific about reading the word at encoding), "know" (recognizing the word without any recollective experience), "new," or "unsure" (**Figure 5.1C**) via button presses. Participants had 4 s in total for making a judgment (i.e., 2-s word presentation followed by a fixation point for 2 s).

Following previous studies (e.g., Fenker et al., 2008), participants were not tested on the novel movie sequences, and therefore, they were not informed about a possible relation between the movies and the word-related memory task. All words were taken from a pool of

words and randomly assigned to experimental conditions. Thus, there was no preselection or assignment of words to certain groups or conditions.

The experiment was programmed with Psychophysics Toolbox 3.0.10 (Brainard, 1997) and Matlab (R2014b version) software.

Since the movie rating scale and the MDBF were not implemented from the beginning of the study, in experiment 1 only 55 out of 61 participants filled out the rating scale. From these, the first 37 participants completed the scale on day 2 instead day 1, after finishing the recognition task. In experiments 2 and 3, all participants rated the movies directly after presentation. For the MDBF, 105 out of 182 participants completed the questionnaire: 24 out of 61 participants in experiment 1, 23 out of 60 in experiment 2 and 58 out of 61 in experiment 3.

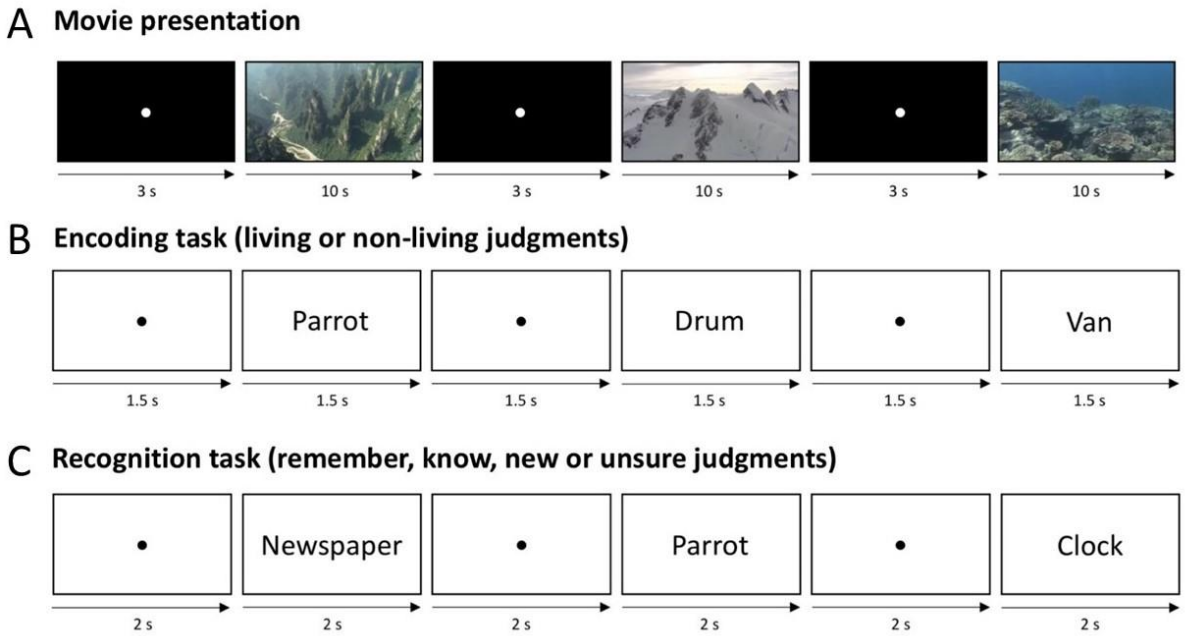

Figure 5.1. Experimental design. (**A**) In all three experiments, subjects watched either novel (NOV group) or five repeating (FAM group) movie clips for 13 min. The movies were presented directly after (experiment 1), 15 min after (experiment 2) or 15 min prior to (experiment 3) encoding. (**B**) During encoding, participants classified nouns into "living" vs. "non-living" by button presses. (**C**) On the second day, all 100 words from the encoding phase were presented intermixed with 100 new words, and participants classified them into "remember", "know", "new," or "unsure."

5.2.3 Statistical analysis

For the encoding task, hit rates (HRs) were analyzed as the proportion of correct answers (relative to all possible correct answers). For the subsequent recognition task, cHRs of remember (cHR-remember) and know (cHR-know) answers were defined as follows:

$$\text{cHR} = \frac{correct\ hits}{possible\ correct\ hits} - \frac{false\ alarms}{possible\ false\ alarms}.$$

Moreover, RTs were analyzed for the encoding and recognition task. Here, within each subject, RTs of 2 SD above and below the subject's mean were excluded, and the remaining trials were averaged for subsequent between-subjects analyses.

To ensure that groups did not differ at baseline, HR and RT for day 1 (encoding task) were investigated using two-way ANOVAs (3 × 2) with the between-subject factors time point of movie presentation (experiment 1: directly after encoding vs. experiment 2: 15 min after encoding vs. experiment 3: 15 min prior to encoding), and novelty (NOV vs. FAM). The effects of novelty on memory performance for day 2 (recognition task) were investigated using a three-way mixed-design ANOVA (3 × 2 × 2) with the between-subject factors time point (experiments 1, 2, and 3, as above), novelty (NOV vs. FAM), and the within-subject factor memory (cHR-remember vs. cHR-know or RT-remember vs. RT-know).

The relationship between novelty and movie rating was analyzed using a two-way ANOVA (3 × 2). Further, a 3 × 2 × 3 MANOVA with the between-subject factors time point and novelty and the within-subject factor inner state (good mood/bad mood vs. wakefulness/tiredness vs. calmness/restlessness) was conducted for the mental state questionnaire. Finally, post hoc t-tests were used when applicable with a Bonferroni adjusted alpha level of $p = 0.025$ (0.05/2). All statistical analyses were performed using IBM SPSS Version 24.

5.3 Results

On average, participants discriminated living vs. non-living nouns with a mean HR of 0.96 ± 0.02 (minimum 0.9, maximum 1; range 0–1). The mean RT was 884 ± 105 ms. A 3 × 2 ANOVA with the factors time point and novelty on HRs and RTs revealed no main effects and no interactions [HRs: novelty: $F(1,176) = 0.692$, $p = 0.406$, partial $\eta^2 = 0.004$; time point: $F(2,176) = 1.664$, $p = 0.192$, partial $\eta^2 = 0.019$; novelty × time point: $F(2,176) = 0.349$,

p = 0.706, partial η² = 0.004; RTs: novelty: F(1,176) = 2.373, p = 0.125, partial η² = 0.013; time point: F(2,176) = 0.348, p = 0.706, partial η² = 0.004; novelty × time point: F(2,176) = 0.587, p = 0.557, partial η² = 0.007].

For the recognition memory task, a 3 × 2 × 2 ANOVA on cHR-remember and cHR-know revealed no main effects [memory: F(1,176) = 0.295, p = 0.587, partial η² = 0.002; time point: F(2,176) = 0.216, p = 0.806, partial η² = 0.002; novelty: F(1,176) = 0.510, p = 0.476, partial η² = 0.003] and no interactions [memory × time point: F(2,176) = 1.972, p = 0.142, partial η² = 0.022; memory × novelty: F(1,176) = 0.258, p = 0.612, partial η² = 0.001; memory × time point × novelty: F(2,176) = 0.348, p = 0.706, partial η² = 0.004].

Subsequently, two separate 3 × 2 ANOVAs were conducted for both, cHR-remember and cHR-know. Again, no significant main effects or interactions could be observed for cHR-remember [time point: F(2,176) = 0.990, p = 0.374, partial η² = 0.011; novelty: F(1,176) = 0.790, p = 0.375, partial η² = 0.004; novelty × time point: F(2,176) = 0.092, p = 0.912, partial η² = 0.001] or cHR-know [time point: F(2,176) = 1.736, p = 0.179, partial η² = 0.019; novelty: F(1,176) = 0.000, p = 0.986, partial η² = 0.000; novelty × time point: F(2,176) = 0.429, p = 0.652, partial η² = 0.005]. **Figure 5.2** depicts cHR-remember and cHR-know for all three experiments and groups.

A 3 × 2 × 2 ANOVA on RTs (during recognition) showed a main effect of memory [F(1,174) = 127.61, p < 0.001, η² = 0.42], but no other main effects [time point: F(2,174) = 0.102, p = 0.903, partial η² = 0.001; novelty: F(1,174) = 0.078, p = 0.781, partial η² = 0.00]. Post hoc analysis revealed significantly faster "remember" responses in contrast to "know" responses (**Figure 5.3**). There was no significant interaction between novelty and time point [F(1,174) = 0.097, p = 0.755, partial η² = 0.001; F(2,174) = 0.780, p = 0.460, η² = 0.009]. Finally, a memory × time point × novelty interaction also did not reach significance [F(2,174) = 0.228, p = 0.796, partial η² = 0.003].

A 3 × 2 ANOVA on movie ratings revealed a main effect of novelty [F(1,170) = 36.59, p < 0.001, partial η² = 0.177). Post hoc analysis showed that novel movie clips were rated more positive as compared to the familiar movie clips (**Figure 5.4**). The novelty × time point interaction was not significant [F(2,170) = 2.699, p = 0.07, partial η² = 0.031].

A 3 × 2 × 3 MANOVA on ratings of mental states (MDBF) showed main effects of calmness/restlessness [$F(1,99) = 24.536$, $p < 0.001$, partial $\eta^2 = 0.199$] and wakefulness/tiredness [$F(1,99) = 42.041$, $p < 0.001$, partial $\eta^2 = 0.298$; **Figures 5.5A,B**]. Post hoc paired t-tests revealed that in both, the NOV and the FAM group, scores of wakefulness decreased and calmness increased from pre- to post-inner state assessment [NOV: $t(52) = 3.587$, $p = 0.001$; $t(52) = -5.571$, $p < 0.001$; FAM: $t(51) = 6.05$, $p < 0.001$; $t(51) = -2.674$, $p = 0.01$]. Finally, a statistically significant interaction was observed between novelty × good mood/bad mood [$F(1,99) = 6.773$, $p = 0.011$, partial $\eta^2 = 0.064$; **Figure 5.5C**]. Post hoc analysis (paired t-tests) for the NOV and FAM group separately – each averaged across experiments – showed that good mood ratings of the NOV group increased [$t(52) = -4.072$, $p < 0.001$], while good mood ratings of the FAM group did not change [$t(51) = 0.865$, $p = 0.391$].

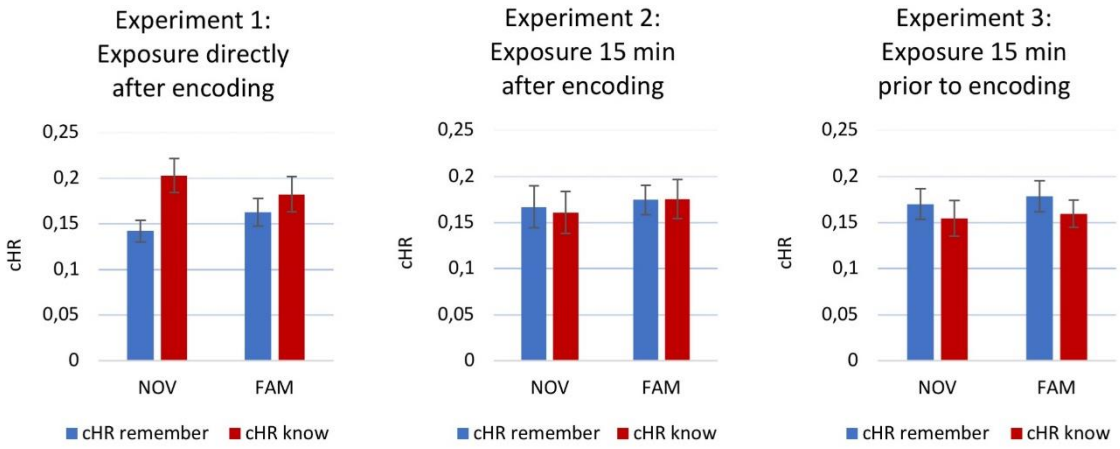

Figure 5.2. Recognition memory performance. Corrected hit rate (cHR) for remember and know for all three experiments. Error bars indicate ±1 standard error of the mean (SEM).

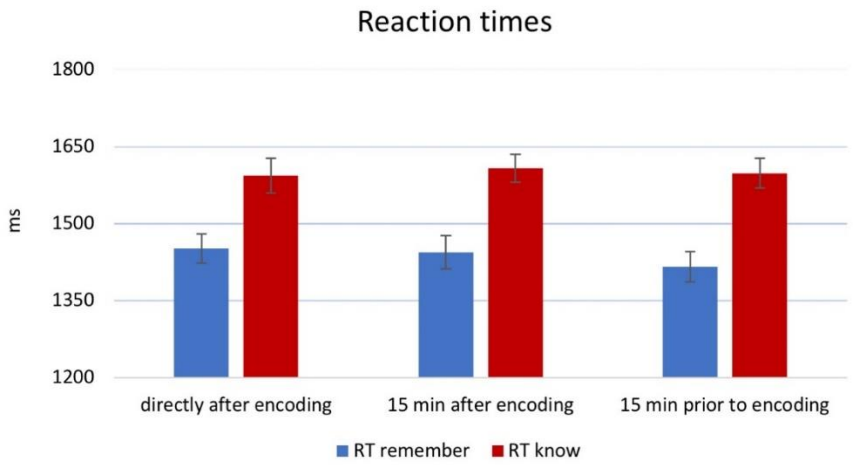

Figure 5.3. Results for RTs at retrieval. Overall, reaction times (RTs) were faster for "remember" than "know" responses (main effect), but there was no significant effect of novelty. For display purposes, groups were combined. Error bars indicate ±1 SEM.

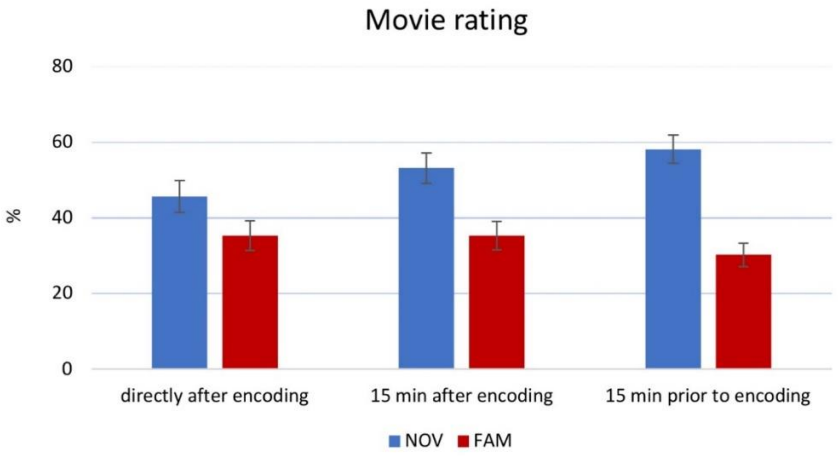

Figure 5.4. Main effect of movie rating. Participants of the NOV group (mean 52.51%) rated movies more positive than participants in the FAM group (mean 33.52%). Error bars reflect ±1 SEM.

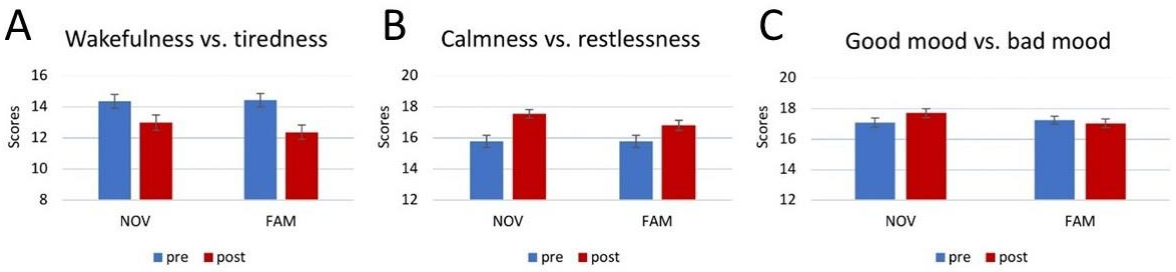

Figure 5.5. Mental state ratings after movie presentation. (**A**) Main effect for wakefulness vs. tiredness. Higher values represent wakefulness, lower values tiredness. (**B**) Main effect for calmness vs. restlessness. Higher values represent calmness, lower values restlessness. (**C**) Interaction between good mood vs. bad mood and group. Higher values represent good mood, lower values bad mood. Increase of good mood in the NOV group, no change in the FAM group.

5.4 Discussion

We investigated whether the exposure to novel nature movies before or after encoding of a word list can improve subsequent LTM performance. Although novel (in contrast to repeated) movies were rated as more interesting and had a more positive effect on mental states, they did not improve LTM in any of our three experiments. Specifically, novel movies right after, 15 min after or before encoding did not affect familiarity- or recollection-based recognition memory scores. Our findings suggest that an exposure to novelty without an active task is not sufficient in order to promote subsequent LTM. In the following, we will discuss several explanations of our null finding, and conclude that a sense of agency with the novel material appears to be necessary in order to induce a positive effect on learning.

On the basis of previous work, we hypothesized that novelty promotes subsequent LTM since it activates the mesolimbic and noradrenergic system leading to DA release into the hippocampus (Lisman and Grace, 2005; Lisman et al., 2011; Duszkiewicz et al., 2019). Therefore, a rather physiological explanation for our null finding is that the employed stimulus material (video sequences) simply did not lead to the cascade of mesolimbic and noradrenergic activity and subsequent DA releases. While there is sufficient evidence that novel scene images activate the SN/VTA, striatum, and hippocampus (Bunzeck and Düzel, 2006; Zaehle et al., 2013; Bunzeck et al., 2014; Herweg et al., 2018), it remains unclear whether the same is true for novel nature movie sequences. Indeed, several forms of novelty have been dissociated previously, further indicating conceptual differences. Specifically, item novelty, contextual novelty and spatial novelty might differ from surprise and contextual deviance in terms of underlying processes and associated cognition. An elegant overview of these and related concepts can be found in (Schomaker and Meeter, 2015).

Along the same lines, novelty can be interpreted in absolute and relative terms, in the sense that expectations about upcoming information drive novelty processing. For instance, within the medial temporal lobe, novelty signals adaptively scale according to expected contextual probabilities of new and familiar events (Bunzeck et al., 2010). In other words, when cues predict a familiar but contextually novel item with equal probability, the familiar item leads to similar neural activity as compared to a novel item (in another context). Therefore,

continuously presented familiar and novel movie sequences may have led to similar mesolimbic neural activity due to its adaptive properties, and the repetitive and predictive character of our paradigm. On the other hand, novel movies were, on a subjective level, rated as more interesting than familiar ones (**Figure 5.4**), and this was paralleled by a more positive mental state. Specifically, novel movies induced a better mood as compared to familiar ones. Although this was expected, and is in line with previous findings (Park et al., 2010), there was no apparent effect on subsequent or prior word-learning, which might relate to the relatively small effects of novelty on mood (**Figure 5.5C**). Together, despite a positive subjective effect (interest and mood), it appears possible that the presented novel movie sequences did not lead to neural activity within the mesolimbic system. This hypothesis, however, can only be supported by future studies using fMRI or other appropriate techniques.

A more likely explanation for our null finding of novelty on memory relates to differences in task requirements. In contrast to our experiment, subjects in other studies were actively engaged with the novel material. For instance, in Fenker et al. (2008), subjects had to make an indoor/outdoor discrimination on scene images, which, in the case of novel images, enhanced recollection and free recall of subsequently learned words. In Schomaker et al. (2014), humans actively explored a novel virtual environment, which also enhanced free recall of a subsequently learned word list. In children, the active and attentive participation in a novel science class before or after reading a story improved subsequent memory (Ballarini et al., 2013). Such active engagement with the novel stimulus material is comparable to animal studies, in which rodents are allowed to actively and freely explore a novel (vs. familiar) environment; this promotes hippocampal LTP and also drives learning and memory (Li et al., 2003; Ballarini et al., 2009; Wang et al., 2010a). Further support and possible explanations of a close link between active behavior and learning comes from human studies. They indicate that a sense of agency, for instance through active choices during learning, promotes subsequent declarative LTM, and this effect was related to striatal and hippocampal activity as revealed by fMRI (Murty et al., 2015). Therefore, another parsimonious explanation for our null finding is that a stronger sense of agency, possibly associated with the engagement of memory related brain regions, is necessary in order to induce a positive effect of novelty on LTM. This

hypothesis should be further investigated and has potentially important implications for possible interventions, which would need to include an active novelty manipulation.

A third possible explanation for our null finding relates to the length and onset of the novelty experience. Regarding the length, at least one animal study suggests that a 5-min novelty exploration is most efficient to induce LTP (Li et al., 2003); therefore, in subsequent human studies, novelty was presented for 5 min (Fenker et al., 2008; Schomaker et al., 2014). However, in the aforementioned study by Ballarini et al. (2013), a novel science class before learning was 20 min long; and in a study with human adults, a positive effect of novelty on learning has been shown with several repeating learning contexts that were approx. 6 min long (Bunzeck and Düzel, 2006). Finally, a 15-min stay in a novel environment led to a reinforcement of early- to late-LTP in rats (Straube et al., 2003) further suggesting that a limitation of 5 min might not necessarily be justified. In any case, our 13-min novelty presentation did not promote learning, which leaves the optimal length unclear.

In terms of onset, evidence suggests that a close proximity between novelty and the learning task is important. For instance, a weak high-frequency conditioning stimulation only induced LTP when rats explore a novel environment 5 min before, but not 1 day before stimulation (Li et al., 2003). In humans, a novel science lesson only promoted learning when it was experienced 1 h before or after, but not 4 h before or after reading a story (Ballarini et al., 2013).

In our study, novelty experience and learning were close in time, but there was no positive effect on memory. Together with the systematic variation (novelty before and after learning), this suggests that other factors (sense of agency in particular) may more likely explain our null finding. In our study, recognition memory was tested 1 day after encoding. This delay was based on previous work with a time window of 24 h between encoding and recollection due to the effect of DA on the late phase of LTP (Wittmann et al., 2007; Lisman et al., 2011). However, previous studies also revealed memory improvements by novelty after a short delay (Bunzeck and Düzel, 2006; Schomaker et al., 2014), which leaves it open whether novel movies have an effect on learning right after encoding.

Previous novelty studies differ in the way how memory is being tested. Here, we used a remember/know paradigm in order to differentiate the potential effects of novelty on

hippocampus related recollection vs. rhinal cortex-related familiarity. While Schomaker et al. (2014) have used hippocampus-dependent free recall and found a positive effect of novelty on learning, Fenker et al. (2008) could show that free recall and recollection was improved by novelty. Therefore, it appears unlikely that free recall would have revealed a positive effect in our study. However, future studies might include other, more hippocampus-dependent recall and learning tasks, such as spatial navigation, to further pinpoint the exact conditions under which novelty promotes memory.

As expected, RTs were shorter for "remember" as compared to "know" responses (**Figure 5.3**). This is in line with previous studies showing that RTs for items that are associated with recollective experiences are typically faster as compared to those without recollective experience (Dewhurst et al., 2006; Rotello and Zeng, 2008; Gimbel and Brewer, 2011). While, at the first glance, this may not be compatible with dual-process models, suggesting that familiarity is a more rapid process than recollection (Jacoby, 1991; Yonelinas, 2002), the slower RTs for "know" responses might reflect difficulties in old judgments without the retrieval of contextual details (Henson et al., 1999); this also fits to the notion of "remember" responses having an all-or-none quality, while "know" responses require a post-retrieval processing to determine their familiarity (Dewhurst and Conway, 1994; Dewhurst et al., 2006). In any case, our findings do not provide evidence that novelty exposure impacts on either form of recognition memory. This has been expected for "remember" responses in particular, given its closer link to the hippocampus (Diana et al., 2007), which receives dopaminergic innervations (Lisman and Grace, 2005). However, our finding must be interpreted with the limitations and possible explanations mentioned above; therefore, they do not rule out that novelty does selectively impact on "remember" responses, for instance, when an active task on the novel material is employed.

Together, novel movie sequences were perceived as more interesting and led to better mood as compared to familiar movies. However, novelty exposure before or after learning a word list did not promote recollection- or familiarity-based recognition memory. This is incompatible with previous studies in humans and animals, which could show a positive effect of novelty exposure on LTP and LTM. Our findings suggest that a simple exposure to novelty

is not sufficient to promote learning; instead, an active task with the novel stimulus material appears important. This hypothesis has important implications for possible interventions, and, therefore, needs to be tested in future studies.

General discussion

- Summary of findings
- Structural integrity of the BG impacts on behavior
- Challenges of intervention models
- Limitations and future directions
- Conclusion

6 Discussion and conclusion

The objective of the present thesis was threefold: First, to investigate the relationship between structural properties and cognitive functioning in older adults. Second, to analyze the positive effects of a 4-week working memory training and its possible modulation by novel stimuli, and third, the consequences of novelty before and after a word-learning task on recognition memory. In the following, the findings of the three studies will be summarized and integrated. In addition, challenges of intervention models and how to overcome these obstacles will be discussed. Finally, limitations and future directions are presented.

6.1 Summary of findings

In study 1 (Biel et al., submitted), we aimed to investigate the relationship between cognitive performance and structural integrity of the BG, with a focus on GM volume, myelin (i.e., MT), and iron (i.e., R2*). Consequently, the baseline data (t1) of 79 healthy older adults who participated in a cognitive training study were analyzed. Using VBM and VBQ, age-related declines in GM volume and MT, and an age-related increase of R2* levels within the BG were revealed. Moreover, we detected that both, R2* and demyelination (as indicated by MT), negatively correlated with performance in verbal memory and executive functioning. Within the SN/VTA, age-related demyelination but no further link between age, iron, and behavior was observed.

In study 2 (Biel et al., 2020), we followed previous work on cognitive training in older adults and used a well-established working memory task. We investigated whether a 4-week training of a 2-back task in 83 healthy older adults improves a) abilities of the trained task, and b) performance in untrained cognitive domains. Since the processing of novelty can advance subsequent memory performance, we further tested whether novelty modulates the positive effects of a cognitive training intervention. To that aim, a training task intermixed with short novel nature movie sequences was implemented. The results concurred with previous findings and showed that a 4-week working memory training improves task specific performance (i.e., cHR) and RTs. However, a transfer effect to untrained abilities or a modulation of training or transfer effects by novelty did not emerge. On the neural level, no changes in GM volume, myelin, or iron were observed.

In study 3 (Biel and Bunzeck, 2019) we further examined the effects of passive novelty exposure on subsequent memory performance in younger adults. To that end, three experiments were conducted, in which novelty (i.e., novel nature movie sequences) was presented 15 min before, directly after, or 15 min after the encoding of a word list. The next day, participants performed a recognition memory task following the remember/know paradigm. As a result, RTs for "remember" were faster than for "know" judgements, suggesting a rapid response of the hippocampus-dependent memory. However, there were no novelty-induced differences regarding "remember" (i.e., hippocampus-dependent) or "know" (i.e., hippocampus-independent) judgements between the different time points indicating no timing specific passive novelty effects.

6.2 Structural integrity of the BG impacts on mesolimbic and fronto-striatal circuits

In regard to the first goal of this thesis, it was demonstrated that markers of iron and demyelination within the BG not only correlated negatively with performance in verbal memory (Steiger et al., 2016), but also in executive functioning (study 1). This finding underlines the sensitivity of BG integrity and shows that not only the hippocampal-VTA-loop is affected by BG iron and demyelination but also the fronto-striatal pathway.

As explained in detail in section 1.5, the hippocampal-VTA loop (**Figure 1.1**) enables the transmission of novel information into LTM storage (Lisman and Grace, 2005). Hence, we suggested that BG iron which has been found to negatively correlate with performance in verbal memory (Steiger et al., 2016), disrupts the connection of this loop. Our observation that BG iron and demyelination also impair executive functioning, which is associated with frontal areas (i.e., dorsolateral PFC, orbital frontal, and anterior cingulate cortex; Tekin and Cummings, 2002) can be explained by a similar mechanism.

The fronto-striatal circuit forms a closed loop involving the PFC, the BG, the SN/VTA, and the thalamus. The transmissions from one region to another, are mediated via excitatory glutaminergic and inhibitory GABAergic neurotransmissions. Specifically, via excitatory glutaminergic neurotransmission, a signal is sent from the PFC to the striatum. From here, an inhibitory GABAergic signal is sent via the pallidum to the SN/VTA and continues to the thalamus. Following, an excitatory glutaminergic transmission returns to the PFC (**Figure 6.1**).

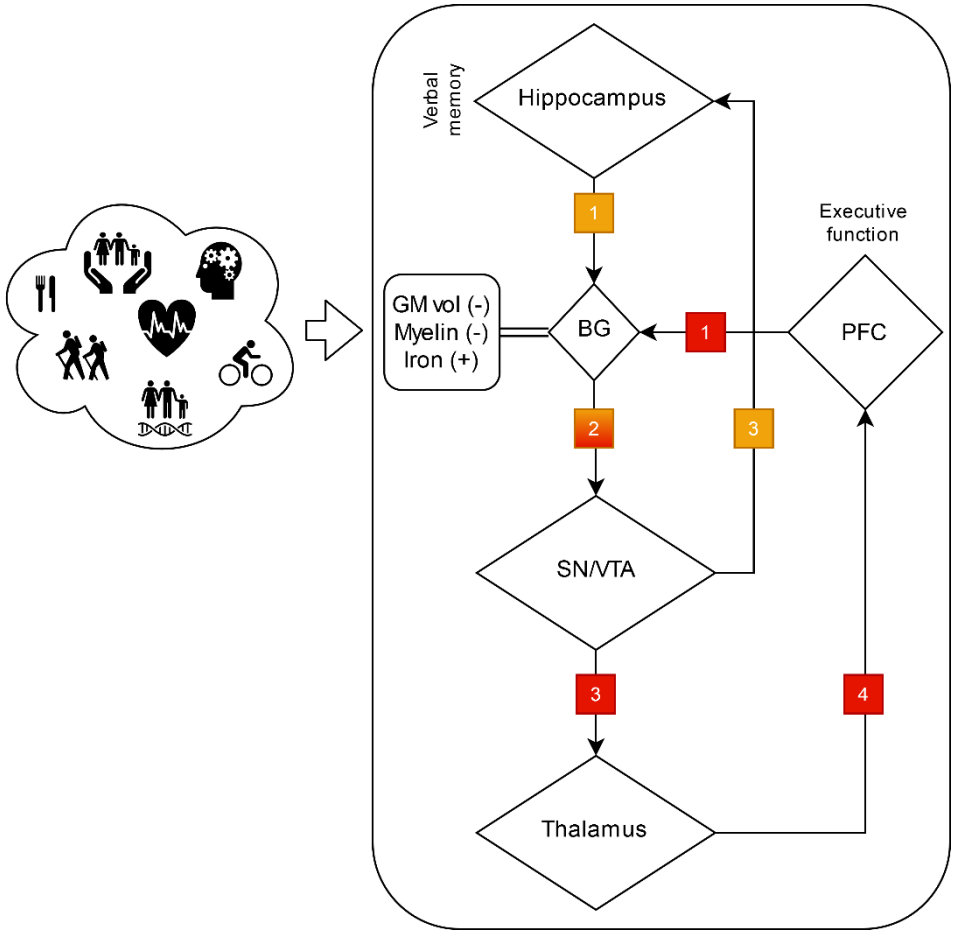

Figure 6.1. Simplified schematic diagram of the dopaminergic systems which are affected by age-related iron increase and demyelination of the basal ganglia (BG).The numbers refer to the order of information processing; the numbers within orange squares display the mesolimbic pathway (i.e., hippocampal-VTA-loop) and numbers within red squares the fronto-striatal pathway. Structural integrity of the BG might be influenced by several factors, including cognitive fitness, environmental enrichment, social involvement, physical activity, diet, cardiovascular health, and genetics (as shown on the left side). Changes of specific lifestyle factors could lead to an attenuation of age-related reductions in GM volume and myelin, as well as age-related iron increases, and in turn, improve cognitive performance.

Within this circuit, the neurotransmitters DA, acetylcholine, serotonin, glutamate, and GABA mediate cognition (Alexander et al., 1986; Alexander and Crutcher, 1990; Tekin and Cummings, 2002). As a consequence, disturbances of the fronto-striatal circuit can cause severe impairments in executive functioning and cognitive flexibility (Tekin and Cummings, 2002; Bonelli and Cummings, 2007). Along the same lines, Parkinson's disease is associated with impaired executive functioning (Grahn et al., 2008; Leh et al., 2010; de la Fuente-Fernández, 2012), possibly caused by increased iron levels (Wang et al., 2016; Thomas et al., 2020) which

interrupt the fronto-striatal circuit (Kalpouzos et al., 2017). Moreover, in Huntington's disease, which is also strongly linked to BG dysfunction, striatal atrophy correlates negatively with functional connectivity of the fronto-striatal network (Turner et al., 2016). Notably, deficits of the fronto-striatal circuit are also related to a variety of psychiatric disorders, ranging from apathy to impulsivity (Bonelli and Cummings, 2007). Hence, besides the observed executive dysfunction, a disturbance of the fronto-striatal system could result in age-related psychiatric impairments which were beyond the scope of this study.

Although the parameters of GM volume, myelin, or iron levels were not modulated by the 4-week cognitive training, other lines of research suggest that structural, functional, and behavioral aspects could be influenced by external factors. Interestingly, environmental enrichment was shown to enhance structural integrity (Kühn et al., 2017), and positively modulate cognitive reserve in aging as revealed by animal models (Sampedro-Piquero and Begega, 2017). Similarly, encoding of novel working memory stimuli was linked to increased activity within the BG and the fronto-striatal network (Geiger et al., 2018). Using fMRI, the authors revealed increased activations within the striatum when novel working memory items were processed. Moreover, novel items enhanced connectivity between the dorsolateral PFC and the striatum (Geiger et al., 2018). These findings emphasize once more the importance of stimulus relevance of novelty in stimulating dopaminergic modulation and suggest a positive influence of novel stimuli not only on the mesolimbic, but also the fronto-striatal network.

In addition to an enriched environment and novelty, health aspects, such as a balanced diet (Gómez-Pinilla, 2008; Luciano et al., 2017; Chianese et al., 2018) or physical activity (Verstynen et al., 2012; Niemann et al., 2014) have been positively linked to brain health and cognition. Moreover, physical exercises were related to greater BG volume in older adults (Erickson et al., 2010; Verstynen et al., 2012; Niemann et al., 2014). It has been proposed that metabolic changes and increased blood perfusion mediate the positive effects of physical activity and neurogenesis (Kojda and Hambrecht, 2005; Holschneider et al., 2007; Pereira et al., 2007). In contrast, hypertension and obesity were related to volume loss (Raz et al., 2007; Ronan et al., 2016) but also to higher iron contents within the striatum (Rodrigue et al., 2011; Blasco et al., 2014; Daugherty et al., 2015). Interestingly, exercise training of only 20 min could increase

hippocampal blood flow (Steventon et al., 2020), further stressing that sufficient blood supply seems to be a relevant mediator of structural integrity and cognitive performance.

Hence, a manipulation of lifestyle factors (e.g., environmental enrichment, physical activity, healthy diet, sufficient sleep) could positively influence structural integrity and functional efficiency of the BG, and therefore, improve performances which are not only dependent on the hippocampal-VTA-loop, but also the fronto-striatal circuit. Although it is yet an open question, to which extend lifestyle factors can mediate GM volume, myelin, and iron levels, we could demonstrate that iron as well as myelin levels influence performance in verbal memory and executive functioning. Further research is necessary to uncover potential implications for intervention models. A suggestion of this model is depicted in **Figure 6.1**.

6.3 Challenges of cognitive intervention models

The second and third goal of this thesis were to investigate the positive effects of a 4-week working memory training and whether exposure to novelty can improve subsequent memory performance, respectively. However, neither cognitive training nor novelty enhanced cognition. Thus, the positive modulation of cognitive functioning might be more complex than previously thought.

Study 2 revealed that a cognitive training improves performance in the trained task but does not transfer to untrained domains. Possible explanations have been elucidated in detail in the discussion section of study 2. In short, these were a) the implementation of a passive control group, b) differences in the analysis of neuropsychological test scores (i.e., instead of D2-R BZO we used the more robust KL value), c) the application of a non-adaptive n-back training, and d) the focus on structural analysis. However, our findings are also in accordance with previous studies which failed to replicate training-induced transfer effects (Owen et al., 2010; Shipstead et al., 2010; Redick et al., 2013; Dougherty et al., 2016), and cast doubts about the effectiveness of cognitive trainings. Moreover, there are several obstacles when designing a cognitive training study. In the following, challenges of cognitive intervention models are discussed and possible ways to overcome these are presented.

The most general criticism tapping on cognitive training paradigms relates to their artificial nature. On the one side, these trainings aim to enhance cognitive performance in older

adults and thereby, improve daily life abilities. On the other side, artificial constructs of cognitive performance are measured. Notwithstanding, a standardized test procedure is necessary to guarantee that test results of cognitive functioning are comparable, but it remains unclear, how well a diagnostic standardized test can be converted into real-life conditions. For instance, executive functioning is often assessed with the TMT. While this test provides a good sensitivity and comparability between the individuals, it is unanswered, whether improvements in the TMT (for instance through cognitive training) are also recognizable in daily life executive functioning. On the first glance, the construct of executive functioning is way more complex than can be tested with the TMT, but studies unfolding this relationship are yet lacking (Chan et al., 2008).

Along the same lines, we revealed that a 4-week working memory training can improve the trained n-back task. However, we cannot make assumptions about the comparability between improvements in the n-back task and daily life working memory skills of the participants. Besides improvements in the trained task, previous studies also observed a transfer to untrained domains, but it is unclear, whether these changes affected daily life cognition. These questions cannot be answered by the present study and need to be addressed in future investigations. Therefore, the assessment of how a standardized test is related to real-life performance within the tested domain seems indispensable.

A recent review casts doubts that cognitive trainings enhance general cognitive functioning (Sala and Gobet, 2019). By conducting a review of several meta-analyses, the authors revealed that the effects on general cognition were marginal and differences in findings between training studies were mediated by differences in study design and statistical analyses. Once more, the authors conclude that the positive effects of cognitive training are restricted to the trained task and thus, different intervention models to improve general cognition should be targeted. Although, a meta-analysis came to the conclusion that working memory training of an n-back task improves fluid intelligence (Au et al., 2015), a re-analysis of the study revealed that the positive effects failed to appear when an active control group was added to the design (Dougherty et al., 2016). Hence, it was suggested that placebo effects influence training outcomes. In the same line, we revealed that improvements in untrained

cognitive domains were mediated by re-test effects, as revealed by a passive control group. The replication crisis underlines the problem of inadequate methodical and statistical analyses in cognitive training interventions. Adequate sample sizes, power, and the implementation of control groups are crucial to obtain reliable results, and thus, should be considered beforehand. Moreover, the effect size is an important estimator which should be taken into account when interpreting statistically significant results. In other words, the presence of significance should not be the only parameter to assess the efficiency of a cognitive training intervention.

In the present study design, two experimental groups and one passive control group were included. Besides the experimental group that underwent the novelty-enriched training program, the other experimental group underwent the cognitive training without novelty exposure, and thus, functioned as an active control when testing for the effects of novelty. The passive control group which did not participate in any training, was implemented in order to test for training effects, independent of novelty manipulation. The findings of our study emphasize that training effects are restricted to the trained ability, and transfer effects to retesting. Importantly, neither of them was changed by a 4-week cognitive training nor by novelty manipulation.

The absence of novelty effects (studies 2 and 3) might have several reasons. First, the manipulation of novelty in humans is more complicated compared to animals. While in animals, a realistic representation of novelty can be imitated easily via a novel and enriched environmental setting, in humans, a novelty imitation within experimental settings is more complex. We suggest that passive novelty manipulation as used in the present studies (studies 2 and 3) is not sufficient to promote dopaminergic neuromodulation, and therefore, should be coupled with an active task (e.g., categorization of nature movies) in future investigations. However, it is likely that the highest effect of novelty may originate from realistic forms of novelty which also address motivational future behavior (Düzel et al., 2010). In animals, it was extensively demonstrated that a stimulating environment increases memory performance and protects against cognitive decline (Pham et al., 1999; Moncada and Viola, 2007; Yuan et al., 2012; Hullinger et al., 2015). Nevertheless, studies addressing real-life enriched environments in humans are lacking and it can be challenging to target this kind of novelty in an experimental

setup. However, to unfold effects of real-life novelty on subsequent memory performance, new and innovative techniques should be designed to enable the combination between realistic novelty exposure and testability. The constant technical improvement of VR will allow future studies to imitate the experience of real-life novelty in a testable environment, and thus, might be a promising approach.

In order to combine cognitive trainings with novelty, a similar path should be taken. Cognitive training is only valuable when it is capable of enhancing daily life abilities independent from the laboratory outcome. Hence, as aforementioned, cognitive trainings should target everyday functioning, of course in a standardized form to ensure comparability. One possible approach of a real-life cognitive training intervention intermixed with novelty exposure would be to ask the participant to visit, for instance, an art gallery before a standardized training of a specific daily life ability is performed. An example of such a task could be to memorize a shopping list while doing several distracting tasks (e.g., mathematical calculations) in between.

It is without question that the construction of a real-life cognitive training intervention is very challenging. However, at the end, it might be the only appropriate method to resolve contradictory findings of cognitive training benefits and to answer the decisive question whether everyday cognitive functioning can be enhanced by cognitive trainings. Again, VR might be a capable method which remains to be investigated in future studies.

6.4 Limitations and future directions

The presented work reveals age-related effects on structure and behavior, as well as structure-system-behavior correlates. Nevertheless, our findings must be interpreted considering some limitations which should be addressed in future studies.

As already mentioned in the limitation sections of study 1 and 2, MT and R2* are only indirect marker for myelin (i.e., MT) and iron (i.e., R2*) levels. Although at the current stage, noninvasive imaging techniques for the assessment of iron or myelin are scarce, conclusions regarding myelin or iron should be considered with caution. For instance, R2* is sensitive to both, iron and myelin (Lodygensky et al., 2012; Kor et al., 2019). However, iron concentration

as tested by R2* is higher in GM compared to WM (Langkammer et al., 2010). Thus, we suggest that the assessed R2* within BG GM (study 1) is rather linked to their iron than myelin content.

In addition, GM volume, myelin, and iron levels were examined and interpreted independently from each other, although there is evidence for a close relationship and common pathogeneses between different tissue types and systems. Whereas the question of a common cause of structural alterations was not the main focus of our study and cannot be answered by the applied methods, it can be addressed on the basis of prior work. There is evidence indicating that microstructural changes and oxidative damage might be of particular relevance in both, GM atrophy (Esiri, 2007) and demyelination (Peters, 2002). Interestingly, it was found that striatal volume shrinkage was predicted by its iron content, suggesting a critical interplay between GM and iron (Daugherty et al., 2015). Hence, the different structural parameters should be investigated in relation to each other, and additional combined neuroimaging methods should be applied. Since iron is strongly linked to DA synthesis, the relationship between R2* and DA could be assessed using positron emission tomography (PET) on selective dopaminergic radioligands (Niccolini et al., 2014). Specifically, it would be interesting to measure, whether older adults, who have increased R2* values within their BG, show reduced DA uptake.

A further methodological limitation of study 1 relates to the cross-sectional design. Although we obtained insights into age-related structural changes, we cannot draw any conclusions about development over time or directionalities. Even though longitudinal studies are very time consuming and also face some hurdles (e.g., selectivity bias, drop outs, higher costs), they provide valuable information of individual developments over time and further pinpoint critic phases in the adult life, during which degenerative processes accelerate.

While we limited our research question on structural MRI, functional connectivity potentially also plays a key role in the manifestation of age-related differences in GM, myelin, and iron levels (study 1). For instance, iron accumulations and demyelination negatively impact on verbal memory and executive functioning. Thus, it seems reasonable that impaired structural integrity of the BG alters functional connectivity between brain networks which are linked to the BG. Studies in this regard could reveal novel insights into functional network

alterations between older adults with high compared to low iron levels or demyelination. Hence, resting state fMRI studies are well-suited for investigating the correlation between BG structural integrity, functional connectivity, and behavior.

Functional analysis may also offer deeper insights within the cognitive training study (study 2). While the aim of study 2 was to investigate brain structure in relation to cognitive training, we did not detect structural or behavioral changes after a 4-week working memory training. However, functional effects might have emerged, but were not assessed. For instance, a working memory training which was similar to the one used in the present study led to activation decreases within the right lateral middle frontal gyrus/caudal superior frontal sulcus, suggesting increased functional efficiency (Heinzel et al., 2016). Therefore, it is arguable that despite the absence of structural changes, functional changes could have occurred.

Moreover, several studies proposed that cognitive reserve may account for inter-individual differences in cognitive performance in higher age. Education has been shown to be a robust mediator of reserve and thus, could be examined in further analysis. For instance, one could measure the predictive value of education for the relationship between structural integrity and cognitive performance. Interestingly, within patients of Alzheimer's disease that were on the same cognitive level, the high educated group show increased Alzheimer's pathology compared to patients with lower education (Stern et al., 1992). Moreover, engagement in life-time activities show similar effects on Alzheimer's pathogenesis (Scarmeas et al., 2003). These findings suggest that cognitive reserve enables similar or even better performance despite increased brain pathology (e.g., GM atrophy, iron accumulation, demyelination). Therefore, factors of cognitive reserve (i.e., education, intelligence, engagement in life-time activities) should be included in future studies.

Along the same lines, lifestyle factors have been shown to account for inter-individual differences in healthy aging. Specifically, decreased risks of cognitive decline were revealed in individuals who are cognitively engaged (James et al., 2011; Tang et al., 2018), physically active (Gallaway et al., 2017), or on a healthy diet (Smyth et al., 2015). Importantly, hypertension, metabolic and vascular predisposition, and obesity are associated with higher iron contents within the striatum (Rodrigue et al., 2011; Blasco et al., 2014; Daugherty et al., 2015), but also

volume shrinkage across the brain (Raz et al., 2007; Ronan et al., 2016). Moreover, physically active older people show larger hippocampi volume which in turn was related to better memory performance (Erickson et al., 2009). Another factor possibly explaining inter-individual structural differences, is the gender: Compared to women, men show a higher predisposition to iron accumulation (Bartzokis et al., 2007), accompanied by an earlier onset of neurodegenerative diseases (Bartzokis et al., 2004). Although lifestyle and cardiovascular parameters were not included in the present study, this should be addressed and investigated in forthcoming research. For instance, possible influences on structural integrity could be examined by using a longitudinal design with regular MRI assessments and questionnaires that target individual environmental, lifestyle, and health factors.

With this in mind, a multimodal cognitive training could be the preferable cognitive intervention approach. Lifestyle factors play an important role in structural integrity. Cognitive stimulation (Schooler and Mulatu, 2001; Wilson et al., 2010; Volkers and Scherder, 2011), exercises (Rebelo-Marques et al., 2018) or a restricted diet (Sohal and Weindruch, 1996; Luchsinger et al., 2002; Mattson, 2003; Scarmeas et al., 2018) have beneficial effects on healthy brain aging. Combining cognitive, social, and physical aspects, could initiate neural changes that are necessary for effective intervention outcomes. With the focus on capturing the whole picture, also interviews or questionnaires should be applied.

Passive novelty exposure did neither improve the effects of a 4-week working memory training (study 2) nor subsequent memory performance of a word list in younger adults (study 3). In contrast, previous studies detected a positive effect of novelty after the presentation of novel images (Fenker et al., 2008). Nevertheless, it might be arguable, to which extent laboratory novelty is comparable to real-life novelty, which is strongly linked to motivational behavior (Düzel et al., 2010). It seems likely that realistic novelty which is characterized by stimulus relevance and vividness leads to increased DA release compared to artificial novelty exposure in a laboratory condition. In this regard, VR could potentially represent a promising method. As it was demonstrated before, the exposure to VR could enhance motivational and recall performances (Schomaker et al., 2014). With the technical progress, realistic VR settings could regard as a compromise between real-life and laboratory novelty exposure. In addition,

with the use of fMRI, neural activity induced by different modalities of novelty (e.g., visual vs. auditory) but also different kinds of presentation (e.g., images vs. movies) should be measured to reveal the best suited novelty stimuli for future studies. Another important factor might be that the exploration of an enriched environment is coupled with spatial navigation. Hence, hippocampal activation to spatial novelty should be compared with other types of novelty, for instance, stimulus novelty (Schomaker and Meeter, 2015). In addition, differences between exploration and exposure may also account for motivational differences in novelty processing, and therefore, should be considered in future studies.

6.5 Conclusion

Our findings provide novel insights into micro- and macrostructural characteristics in the aging brain and demonstrate that iron accumulation and demyelination impact on performance in verbal memory and executive functioning in healthy older adults. Moreover, we revealed that benefits of a 4-week working memory training are restricted to the trained task and do not transfer to untrained cognitive domains. Although previous studies show that active novelty can improve subsequent memory performance, our findings suggest that passive novelty exposure is not sufficient to modulate the positive effects of cognitive training or to improve subsequent memory performance. Future studies should target personalized factors (e.g., education, lifestyle, health) and analyze how these can contribute to structural integrity, behavioral performance, and inter-individual differences. Increasing knowledge of these factors could find its implication in multi-modal intervention models of cognitive decline.

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