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THE RELATION AMONG AGING, DOPAMINE-REGULATING GENES, AND NEUROCOGNITION

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The relation among aging, dopamine-regulating genes, and neurocognition

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ABSTRACT

When people are getting old, they often feel increasingly harder to concentrate, and become slower and more inflexible during tasks that involve focused attention, information maintenance in the face of distractions, and when fast switching according to changing goals is required. These cognitive functions are collectively referred to as working memory (WM). Both cross-sectional and longitudinal studies have reported WM impairment in aging. Moreover, aging is accompanied by alterations in brain structure, brain function, and dopaminergic neurotransmission. This thesis sought to link WM to brain structure, brain function, and dopamine (DA)-related genes in large samples of younger and older adults. The chief aims were to provide neural and genetic evidence to increase our understanding of the mechanisms of age-related deficits in WM.

The *DRD2/ANKK1*-Taq1A polymorphism has been associated with DA D2 receptor densities in caudate. In **study I**, we investigated the effects of this polymorphism on grey-matter (GM) volume in striatum in older adults, and examined whether the genetic effect interacts with age. Results showed that the A allele of the *DRD2/ANKK1*-Taq1A polymorphism was associated with smaller GM volume in caudate and this effect was only observed in older adults (>72 years).

The *DRD2*-C957T polymorphism has been linked to DA D2 receptor densities in both striatum and extrastriatal areas, such as in prefrontal cortex (PFC). In **study II**, we investigated the genetic effects of two *DRD2* polymorphisms on WM functioning and examined how these effects may interact with adult age. In comparing younger and older adults, we found that the old had lower caudate activity in a highly demanding WM task. In addition, there were single and joint genetic effects of the two *DRD2* polymorphisms on WM performance and frontostriatal brain activity. The genetic effects on brain function were observed in older, but not in younger adults, suggesting magnified genetic effects in aging.

In **study III**, we related white-matter integrity with WM performance in a large sample across a wide age range. Results demonstrated that WM was associated with white-matter integrity in multiple tracts, indicating that WM functioning relies on global structural connections among multiple brain regions. Moreover, white-matter integrity could partially account for the age-related difference in WM. The *COMT*-Val158Met polymorphism has been associated with PFC DA levels. In this study, we found genetic effects of *COMT* on white-matter microstructure, suggesting a relation between dopaminergic function and white-matter integrity.

In **study IV**, we investigated changes of white-matter integrity and WM performance using longitudinal data. We found that white-matter integrity declined across 10 years in the whole sample (25-80 years) and the decline was greater for older than for younger adults, reflecting a non-linear relation between age and white matter. More importantly, we found change – change associations of white-matter integrity and WM performance in several tracts

including genu and body of corpus callosum and superior longitudinal fasciculus, suggesting that impaired WM performance in aging might reflect age-related decrease of white-matter integrity in these tracts. Collectively, these studies demonstrate age-related differences and changes in brain structure and brain function associated with impaired WM performance in aging. The findings support and extend previous work on the roles of DA in WM functioning and brain integrity in aging, and contribute to our understanding of neural and genetic correlates of WM, and how these are affected in aging.

LIST OF SCIENTIFIC PAPERS

I. **Li, X.**, Papenberg, G., Kalpouzos, G., Bäckman, L., and Persson, J. (2018). Influence of the DRD2/ANKK1 Taq1A polymorphism on caudate volume in older adults without dementia. *Brain Structure and Function*, 223(6), 2653-2662.

II. **Li, X.**, Bäckman, L., and Persson, J. (2019). The relationship of age and DRD2 polymorphisms to frontostriatal brain activity and working memory performance. *Neurobiology of Aging*, *84*, 189-199.

III. **Li, X.**, Salami, A., Bäckman, L., and Persson, J. White-matter integrity and working memory: Relationships to aging and dopaminerelated genes. *Manuscript.*

IV. **Li, X.**, and Persson, J. Age-related changes in white-matter integrity and their associations with decline in working memory. *Manuscript.*

CONTENTS

LIST OF ABBREVIATIONS

AD	axial diffusivity
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BET	Brain Extraction Tool
COMT	Catechol-O-methyltransferase
DA	dopamine
DARTEL	Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra
DLPFC	dorsolateral prefrontal cortex
DTI	diffusion tensor imaging
FA	fractional anisotropy
FMRIB	Functional Magnetic Resonance Imaging of the Brain
FSL	FMRIB Software Library
FWE	family-wise error
GAMM	generalized additive mixed model
GLM	General linear model
GM	grey matter
ICV	intracranial volume
MD	mean diffusivity
MNI	Montreal Neurological Institute
NAC	narrow age cohort
PALM	Permutation Analysis of Linear Models
PET	positron-emission tomography
PFC	prefrontal cortex
RD	radial diffusivity
ROI	region of interest
SNAC-K	Swedish National Study on Aging and Care in Kungsholmen
SNP	single nucleotide polymorphism
SPM	Statistical Parametric Mapping
TBSS	tract-based spatial statistics

TFCE	threshold-free cluster enhancement
VBM	voxel-based morphometry
VTA	ventral segmental area
WM	working memory

INTRODUCTION

Working memory (WM) refers to the temporary storage and maintenance of information no longer present in the external environment or just retrieved from long-term memory, as well as the manipulation or updating of this information to guide behavior. WM underlies most complex cognitive functions, such as reasoning and language acquisition, and is critical to many activities in our daily living. Both longitudinal (Charlton et al., 2010; Hultsch et al., 1992) and cross-sectional (Head et al., 2002; Kennedy and Raz, 2009a; Nyberg et al., 2014; Park et al., 2002; Peters et al., 2014) studies have found marked decline in WM during healthy aging. With the development of neuroimaging techniques, researchers have investigated the neural mechanisms underlying age-related WM decline. Potential neural correlates include brain structure, especially white matter, brain function, and neurochemical factors (e.g., DA signaling). In the following two sections, I will give a short background of WM and (1) related brain functions, (2) brain structure, especially white matter integrity, and (3) the dopaminergic system. The following literature review will focus on (1) age-related differences and changes in WM; (2) age-related alterations in brain structure, brain function, and the dopaminergic system, and (3) how these two factors relate to each other.

Dopaminergic modulation may influence WM performance through its effect on brain structure and brain function. For example, age-related differences in functional brain activity has been linked to age-related difference in brain white matter integrity (Persson et al., 2006) and dopamine functioning (Bäckman et al., 2011; Fischer et al., 2010), and brain volumes has been associated with DA binding potential in midbrain (Woodward et al., 2009). Thus, studies including both DA data and brain imaging data during WM would provide complementary information and have implications for the relationship among DA, brain structure and function, and aging of WM. However, this kinds of studies are costly and time-consuming, and the few extant studies suffer from low statistical power due to small sample sizes. There are several genetic polymorphisms that have been associated with dopaminergic functions. DA-related genetic data can be used as an indirect measure of DA levels in the brain. Therefore, genetic imaging studies which combine genetic data with brain imaging data can provide not only insight into the genomic and molecular underpinnings of a cognitive phenotype, but also address questions of mechanisms of cognitive aging. In section 3, I will briefly summarize the effects of DA-related genes on WM, brain structure, and brain function in both young and old samples.

Working memory

According to Baddeley's multi-component model, WM includes two short-term memory buffers, which are specialized for the maintenance of speech-based and visuospatial information, respectively. In addition to these buffers, WM also includes a central executive that controls and manipulates the information in the two buffers. More recently, state-based models are widely accepted (D'Esposito and Postle, 2015; Eriksson et al., 2015). These models assume that WM refers to a capacity-limited state, in which attentional resources are allocated

to internal representations. The internal representations include perceptual or semantic information from either external stimuli or are based on long-term memory. Since the represented information is vulnerable to goal-irrelevant stimuli, focused attention is the core function to maintain and manipulate information, and to flexibly reallocate attention to new information when the goal is updated.

WM interacts with many other cognitive functions. For example, episodic memory refers to the conscious remembrance of events located in time and place (Tulving, 1972). Successful episodic memory requires executive function, an important component of WM, to combine different items (e.g. face–name, object–location) and encode them into long-term memory. Another example is processing speed, which is measured based on the time used to complete a cognitive task with relatively low or moderate complexity (Salthouse, 2000). Processing speed and WM are highly correlated (Ackerman et al., 2002; Waters and Caplan, 2005), and some task paradigms used to assess processing speed are similar to WM maintenance tasks, although the two cognitive domains differ in functional and structural neural correlates (Ackerman et al., 2002; Chen and Li, 2007). The current thesis mainly focuses on WM, but behavioral performance in other cognitive domains is also included in the studies.

Brain functions underlying working memory

Prefrontal cortex (PFC) is critical to maintaining information during WM tasks. For example, in a series of landmark animal studies, PFC neurons demonstrated sustained activity during a delay period between stimulus presentation and subsequent responses in monkeys (Funahashi et al., 1989; Fuster and Alexander, 1971; Kubota and Niki, 1971). With the advent of functional MRI, brain activity in PFC has been found during WM maintenance in humans (Chee, 2004; Courtney et al., 1998; Curtis and D'Esposito, 2003; Rypma and D'Esposito, 2000) and the magnitude of the PFC activity has been associated with WM performance (Curtis and D'Esposito, 2003). Normal WM performance, especially when distraction was present, was affected in patients with lesions in PFC (D'Esposito and Postle, 1999), and in normal participants when transcranial magnetic stimulation was administered to suppress the PFC (Feredoes et al., 2011). Parietal cortex is also strongly involved in WM (Collette et al., 2005; Koenigs et al., 2009), and interacts with PFC to apply cognitive control during WM (Kastner and Ungerleider, 2000).

PFC maintains information not through storing the representation itself but rather, together with parietal cortex, provides top-down control of other brain regions where the information is actually stored (Corbetta and Shulman, 2002; Postle, 2015; Rypma and D'Esposito, 2000). These brain regions include visual cortex (visual representations), parietal cortex (spatial representations), premotor cortex (motor representations) and temporoparietal cortex (verbal and semantic representations). Thus, regional involvement in WM varies according to the type of information to be maintained.

In addition to the neocortex, subcortical regions, especially basal ganglia also plays an important role in WM. Basal ganglia consist of the striatum (caudate nucleus and putamen),

the globus pallidus, the ventral pallidum, the substantia nigra, and the subthalamic nucleus. Globus pallidus has been shown to work together with PFC to exert cognitive control and to filter irrelevant information during WM (McNab and Klingberg, 2008). Striatum, especially the dorsal striatum (caudate nucleus and putamen) has been associated with flexible updating of representations during the tasks (Aron et al., 2003; Cools et al., 2004; Dahlin et al., 2008; Lewis et al., 2004; Madden et al., 2004b; O'Reilly and Frank, 2006). According to much computational work, basal ganglia are engaged in a dynamic gating function, where "Go" or "NoGo" signals are sent from basal ganglia to PFC to either trigger fast updating or keep robust maintenance of information (O'Reilly and Frank, 2006). The distinct role of PFC and striatum will be elaborated more in the following sections. In addition to basal ganglia, hippocampus has been involved in WM, although the findings are somewhat inconsistent. For example, patients with hippocampal lesions has demonstrated comparable (e.g. Baddeley et al., 2010) or lower WM performance (e.g. Olson et al., 2006) than controls in WM tasks in different studies. Yonelinas (2013) suggested that hippocampus might be involved in WM operations that require complex information bindings and retrieval of these associations. Thus, the engagement of hippocampus in WM might depend on the specific tasks used to measure WM.

As alluded to above, WM relies on dynamic interactions among multiple brain regions (for a review, see Rottschy et al., 2012). For example, functional connectivity has been documented between fronto-striatal networks and other regions associated with encoding and storing certain types of information (e.g., visual cortex, parietal cortex; Burzynska et al., 2011; Gazzaley et al., 2004).

The relationship between brain structure and working memory

The relationship between grey matter (GM) volume and WM remains controversial. Some studies have observed positive associations between WM and both global and regional brain volumes, including the PFC, visual cortex, parietal cortex, limbic cortex, hippocampus and striatum (Chee et al., 2009; Gunning-Dixon and Raz, 2003; Head et al., 2002; Raz et al., 2000, 1998). However, other studies did not find any relationships between brain volumes and WM (Ylikoski et al., 2000), and some studies even reported negative associations (Salat, 2002; Van Petten, 2004).

White matter is mainly made of myelinated axons that connect different brain regions. Since working memory requires cooperation of many cognitive processes and involves many brain networks, white-matter structural properties might have an influence on WM. Compared to the measures of macrostructural integrity, such as brain volume or white-matter lesions, white-matter integrity reflects more subtle microstructural properties of white matter. Diffusion tensor imaging (DTI) is a technique that can characterize white-matter integrity in vivo. DTI models water diffusion along and perpendicular to the major axis of the white-matter fiber for each voxel. Fractional anisotropy (FA) and mean diffusivity (MD) are two commonly used indices of white-matter integrity. FA, with the value ranging from 0 to 1, denotes degree of difference of water diffusion in three directions regardless of the rate of diffusion. Higher FA values represent more directional diffusion suggesting intact white-matter integrity. MD reflects

averaged diffusivity in three directions. Higher MD values are related to faster water diffusion, thereby indicating relatively impaired white-matter integrity caused by local myelin injury and axon loss. MD values represents weighted average values of axial diffusivity (AD) and radial diffusivity (RD), which measure the diffusion in the major direction along the white-matter tract, and average diffusions for the other two directions perpendicular to the tract. Higher values of RD and AD reflect poor white-matter integrity. Previous DTI studies have found that individual differences in white-matter integrity have been related to differences in WM (Charlton et al., 2008, 2006; I. J. Deary et al., 2006; Kennedy and Raz, 2009a; Madden et al., 2009b), and processing speed (Bucur et al., 2008; Kuznetsova et al., 2016; Lövdén et al., 2014; Madden et al., 2004a; Salami et al., 2012). The relations of white-matter integrity to WM and speed might be specific to these cognitive domains, as weaker association was found for other cognitive domains, such as episodic memory and verbal ability (for reviews, see Madden et al., 2012, 2009a).

The neurotransmitter dopamine

DA is a neurotransmitter in the brain that is critical to cognition. Dopaminergic neurons in the ventral segmental area (VTA) and substantia project to other cortical and subcortical brain regions. There are several dopaminergic pathways in the human brain. Figure 1 portrays three major circuitries that are associated with cognition. Both the frontal cortex and dorsal striatum contain DA receptors because of the abundant dopaminergic input from midbrain neurons to these regions. DA receptors have five subtypes (D1 to D5), which belong to two subclasses: D1 like and D2 like receptors. DA D1 receptors are found widely in neocortex, especially in the frontal cortex, and striatum, whereas DA D2 receptors have the highest density in striatum and are sparsely distributed in other brain areas.

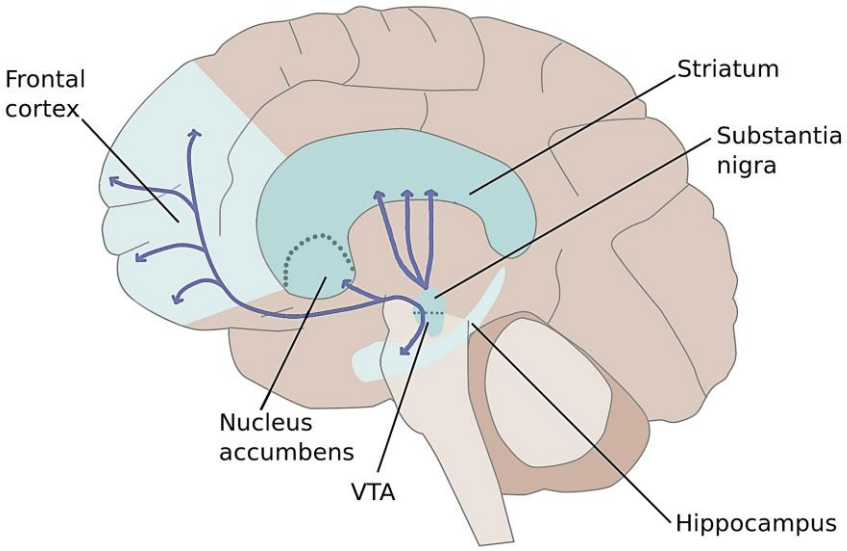

Figure 1. Three major DA pathways. The mesolimbic pathway (from the VTA to the ventral striatum, including nucleus accumbens and the olfactory tubercle), the mesocortical pathway

(from the VTA to the prefrontal cortex) and the nigrostriatal pathway (from the substantia to the dorsal striatum, including caudate and putamen). Credited to Okinawa Institute of Science and Technology Graduate University.

The central role of DA in WM was uncovered in a landmark study by Brozoski and colleagues (1979). This study showed that DA depletion in PFC leads to severe WM impairment. The severity of the impairment was comparable to that seen in monkeys with complete ablations of the PFC (Brozoski et al., 1979). The importance of DA in both PFC and striatum for WM has been substantiated by molecular imaging and pharmacological studies with animals, normal adults, and patients with Parkinson's disease, schizophrenia, and ADHD. Specifically, high DA levels in PFC appears to be important for maintaining stable representations, but could be detrimental in tasks that require fast updating and flexible shifting (Durstewitz et al., 2000; Roberts et al., 1994; Seamans et al., 1998). By contrast, higher striatal DA levels may optimize updating and disrupt maintenance of task-relevant information (Clatworthy et al., 2009; Collins et al., 2000; Floresco and Magyar, 2006; Haluk and Floresco, 2009). Thus, it seems as if successful WM relies on a dynamic balance between stability modulated by PFC DA and flexibility modulated by striatal DA.

Since functional MRI (fMRI) can be used for measuring task-related brain activity, studies that directly measures both on-line fMRI and DA data in the same person could provide insights into the neural mechanism of DA-related effects on WM (Bäckman et al., 2010, 2006). While molecular-imaging studies are still few, they have collectively indicated that associations between DA in caudate and brain function in the PFC (Landau et al., 2009), or in the thalamo-striato-cortical circuit (Salami et al., 2019) are critical for WM functioning. Another way of investigating the relationship between DA and WM is by using dopaminergic agonists/antagonists that directly influence DA levels in the brain. Pharmacological fMRI studies using this approach have found that DA blocking may be associated with lower WM performance, and reduced activity in fronto-parietal regions (Fischer et al., 2010). Overall, empirical data support the view that DA influences WM performance through affecting brain activity in the PFC or striatum.

In addition to studies on functional brain activity, DA D2 receptor levels have been positively related to GM volume in caudate (Woodward et al., 2009). Due to the weak association between brain volume and WM, it remains unclear whether the associations between DA and brain volume can partially account for the associations between DA and WM.

Aging and working memory

Both cross-sectional and longitudinal studies have demonstrated age-related differences and decline in WM (e.g. Gunning-Dixon and Raz, 2003; Head et al., 2002; Hultsch et al., 1992; Kennedy and Raz, 2009a; Park et al., 2002; Peters et al., 2014). Cross-sectional life-span studies have shown that WM increased from childhood until the age of 20 – 30, and decreased afterwards (Park et al., 2002; Peters et al., 2014). However, it should be noted that age effects in cross-sectional research are confounded by cohort difference in factors such as educational

attainment and nutrition level. After correcting for cohort effects, age-related decline in cognition was demonstrated at approximately 60 years, which was the same as that found in longitudinal studies (Rönnlund et al., 2005). Moreover, age-related changes in WM seem to be greater in older than younger adults, suggesting that age trajectories in WM are nonlinear (e.g. de Frias et al., 2007).

The relationship among aging, brain function, and working memory

Age-related differences in WM-induced brain activity have been widely reported. PFC might be the first and most vulnerable brain regions to aging (the frontal-lobe hypothesis of cognitive aging; West, 1996). However, it remains controversial how PFC function changes with age. Some studies found that, compared to younger adults, older adults had lower brain activity in PFC, especially dorsolateral PFC (DLPFC; Rieckmann et al., 2017; Rypma et al., 2001; Rypma and D'Esposito, 2000). However, some studies also found that older adults overrecruited DLPFC compared to younger adults during WM (Eyler et al., 2011; Grady, 2012; Reuter-Lorenz et al., 2000; Spreng et al., 2010). The inconsistency might be reconciled by including different WM loads in the study design (Cappell et al., 2010; Mattay et al., 2006; Nagel et al., 2009; Nyberg et al., 2015, 2009). For example, Nyberg et al.(2015) found that older adults demonstrated greater brain activity in DLPFC in a low-demand WM condition, whereas younger adults had maximal DLPFC activity in a high-demand WM condition. These results suggest low efficiency in modulating PFC activity across changes in WM load in older adults. Age effects on caudate function have been rarely reported, but existing studies are relatively consistent, and reveal lower caudate activity during WM in older compared to younger adults (Madden et al., 2004b; Ziaei et al., 2018).

The relationship among aging, brain structure, and working memory

Both cross-sectional and longitudinal studies have established that global GM volume decline with increasing age (for a review, see Salthouse, 2011). Frontal and parietal cortex seem to yield the largest age-related differences (e.g., Chee et al., 2009; Fjell and Walhovd, 2010; Kennedy et al., 2009a; Raz et al., 2005, 2004) compared to other brain regions, such as occipital lobe. However, past research does not support the notion that age-related changes in brain volumes account for age-related changes in WM functioning (for a review, see Salthouse, 2011). The nature of age-related reduction in brain volume, and how it relates to WM decline in aging remains unclear.

Age-related changes in white-matter integrity have been demonstrated in both cross-sectional (Kennedy and Raz, 2009a; Madden et al., 2017, 2009b; Peters et al., 2014; Salami et al., 2012) and longitudinal (Bender and Raz, 2015; De Groot et al., 2016; Sexton et al., 2014; Teipel et al., 2010) studies. Life-span cross-sectional studies that delineate the age trajectory of white-matter integrity have found that it may increase until around 30 years (20–40 years). After this peak, studies have found both linear (Cox et al., 2016; Lebel et al., 2012; Peters et al., 2014) and nonlinear (Salami et al., 2012; Sexton et al., 2014) decline. Longitudinal studies have demonstrated that the decrease of white-matter integrity is larger in older than younger adults

(Sexton et al., 2014), supporting a nonlinear age-trajectory of white-matter structure in aging. In addition, the decrease of white-matter integrity with age might be greater in frontal compared to occipital brain regions, indicating the white-matter deterioration might follow an anterior – posterior gradient (Davis et al., 2009; Head et al., 2004; Madden et al., 2009b; Salami et al., 2012; Sexton et al., 2014). However, there is no study to date that characterize and statistically compare the age trends of different white-matter tracts across the life span. These questions will be addressed in study IV of the current thesis, using life-span longitudinal data.

From the literature summarized above, two main conclusions can be drawn:(1) Both WM and white-matter integrity decline with increasing age; (2) White-matter integrity is associated with WM independent of age. Here, a key question is whether age-related decline in white-matter integrity can account for age-related impairment in WM. There are several studies to date investigated this question and the results supported the hypothesis (Brickman et al., 2012; Charlton et al., 2010; Madden et al., 2009b). Charlton et al (2010) found that age-related changes in global white-matter integrity over a two-year interval can explain 11 % of the age-related WM decline. Using an ROI approach, FA in genu, splenium, and superior longitudinal fasciculus (Madden et al., 2009b), and FA in inferior longitudinal fasciculus and cerebral peduncles (Brickman et al., 2012) mediated age-related difference in task switching (Madden et al., 2009b) and executive functioning (Brickman et al., 2012). There is no study investigating the spatial pattern of the white matter that can account for the age-related changes in WM. This question will be addressed using a voxel-wise approach in cross-sectional (study III) and longitudinal (study IV) data.

The relationship among aging, dopamine, and working memory

Aging is associated with changes in the dopaminergic system (for a recent review, see Karrer et al., 2017). A common finding is that older adults demonstrate lower striatal D2 receptor binding (Bäckman et al., 2000; Volkow et al., 1998b), and lower D1 receptor binding in both striatal and PFC regions (Bäckman et al., 2011; Rieckmann et al., 2011; Wang et al., 1998) compared to younger adults. Moreover, older adults have lower DA transporter availability (Erixon-Lindroth et al., 2005; Volkow et al., 1998b), and less endogenous DA (Kish et al., 1992) than younger adults. The age effects on DA synthesis capacity varies in different studies. The effect sizes range from -0.80 to 0.64 and no age effect on DA synthesis capacity was found when combining all the studies (Karrer et al., 2017). The relatively preserved DA synthesis capacity in old age might reflect a compensatory function (Karrer et al., 2017), but the underlying mechanism still remains unknown.

Age-related reductions in DA function, including lower D1, D2 receptor densities and DAT, might account for age-related decline in cognition, such as psychomotor function (Wang et al., 1998; Yang et al., 2003), processing speed (Bäckman et al., 2000), episodic memory (Mozley et al., 2001), and WM (Volkow et al., 1998a). For example, studies using positron-emission tomography (PET) have demonstrated an association between D2 receptor binding and cognitive performance, including updating tasks (Wisconsin Card Sorting Test) and other tasks of executive function, such as the Stroop Color Word Test (Volkow et al., 1998a). Studies in

animals have shown that D1 agonists may alleviate WM deficits in aged monkeys with naturally occurring DA depletion in PFC, suggesting an important role of DA receptor stimulation in accounting for age-related decline in cognition (Arnsten et al., 1995).

Given the critical roles of PFC and caudate in WM, and the established associations between white-matter integrity and WM, it is likely that age-related decline in dopaminergic function partially accounts for age-related changes in brain function and structure, especially with regard to white-matter integrity. Several studies have tested this hypothesis by jointly measuring DA D1 receptor binding using PET, and brain activity using fMRI (Bäckman et al., 2011; Nyberg et al., 2016; Salami et al., 2019). For example, Bäckman et al. (2011) found that older adults had reduced DA D1 receptor binding in DLPFC and caudate, lower brain activity in fronto-parietal brain areas, along with impairment in WM performance compared to younger adults. Moreover, controlling for DA D1 receptor binding in DLPFC and caudate can eliminate or partially eliminate the age-related under-recruitment in task-related brain regions during WM tasks (Bäckman et al., 2011). These results indicate an important role of DA in brain and cognitive aging by revealing that DA can mediate age-related changes in brain function during WM. There is no study to date that have explored the relation between DA and different functions of the DLPFC and caudate in WM in an aging population. This question will be addressed in study II of the thesis using DA-related genetic data.

Working memory and dopamine-related genes

There are large differences among individuals in cognitive and brain integrity. Multiple factors contribute to individual differences at behavioral and neural levels, including genetic predispositions, lifestyle factors, epigenetic mechanisms, and their complex interactions. Among these factors, heritability accounts for around 50% of the variance in general cognitive ability, and in the patterns how cognition changes with age (Davies et al., 2011; Deary et al., 2006; Finkel et al., 2005; Tucker-Drob et al., 2014). However, the influence of most single genes on cognition in younger adults may be very small and undetectable (<1% of explained variance), and many genetic studies fail to show robust effects on behavioral performance. It has been argued that measures of brain structure and function may be more sensitive to genetic effects compared to behavioral measures, as brain parameters are more proximal to the underlying molecular mechanisms and therefore more directly affected by a genetic polymorphism (Green et al., 2008).

Individual difference increases with increasing age, which is reflected in cognitive performance, brain function, and brain structure (e.g., Christensen et al., 1999; de Frias et al., 2007; Fandakova et al., 2015; Nelson and Dannefer, 1992; Rönnlund et al., 2005) (Figure 2). The reasons for increased individual differences with increasing age are not fully understood, but one possibility could be that genes exert a larger influence in older compared to younger adults (Lindenberger et al., 2008). An increasing number of studies have found that the genetic effects on cognition are magnified in aging. Such pattern has been reported for *BDNF*, *COMT*, *APOE*, *KIBRA*, *DRD2/ANKK1*-Taq1A, and *DRD2*-C957T polymorphisms (for reviews, see Papenberg et al., 2015c, 2015a). The resource-modulation hypothesis assumes that genetic

influences on cognition are more pronounced for individuals with reduced neuroanatomical or neurochemical resources, such as older adults (Lindenberger et al., 2008). This hypothesis is based on the assumption that the function relating brain resources to cognition is nonlinear, so that genetic differences exert increasingly larger effects on cognition as resources recede from high to medium levels (Figure 3). According to this hypothesis, with loss of brain resources during aging, older adults may benefit more from beneficial genetic predispositions than younger adults. Conversely, younger adults with non-beneficial genetic variants may use their brain resources more efficiently to compensate for genetic disadvantages. Moreover, genetic imaging research extends the observations of magnified genetic effects on cognition and brain function (Persson et al., 2015) to GM volume (Li et al., 2018), and white-matter integrity (Papenberg et al., 2015b).

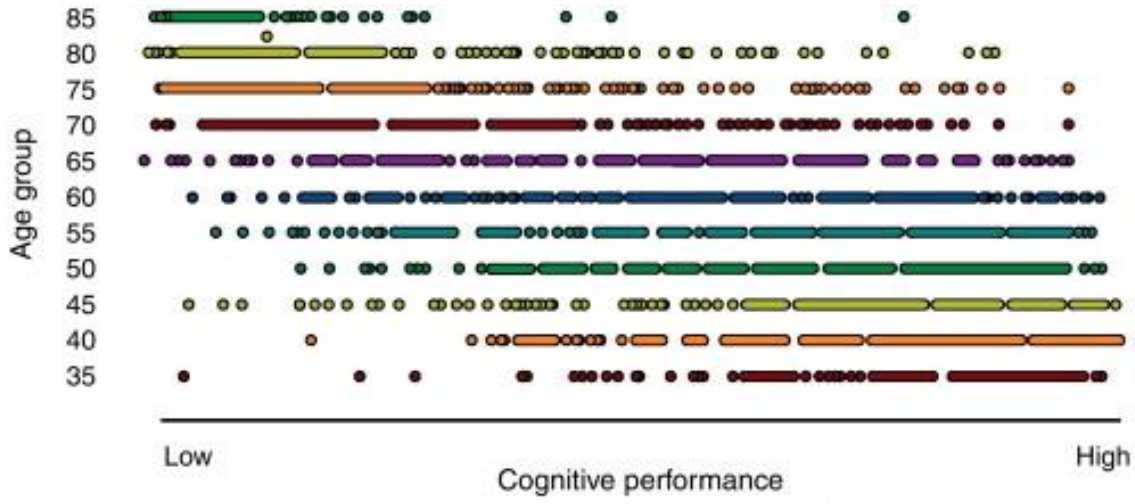

Figure 2. Illustration of individual differences in cognitive performance across the adult span. Adapted from Nyberg et al. (2012)

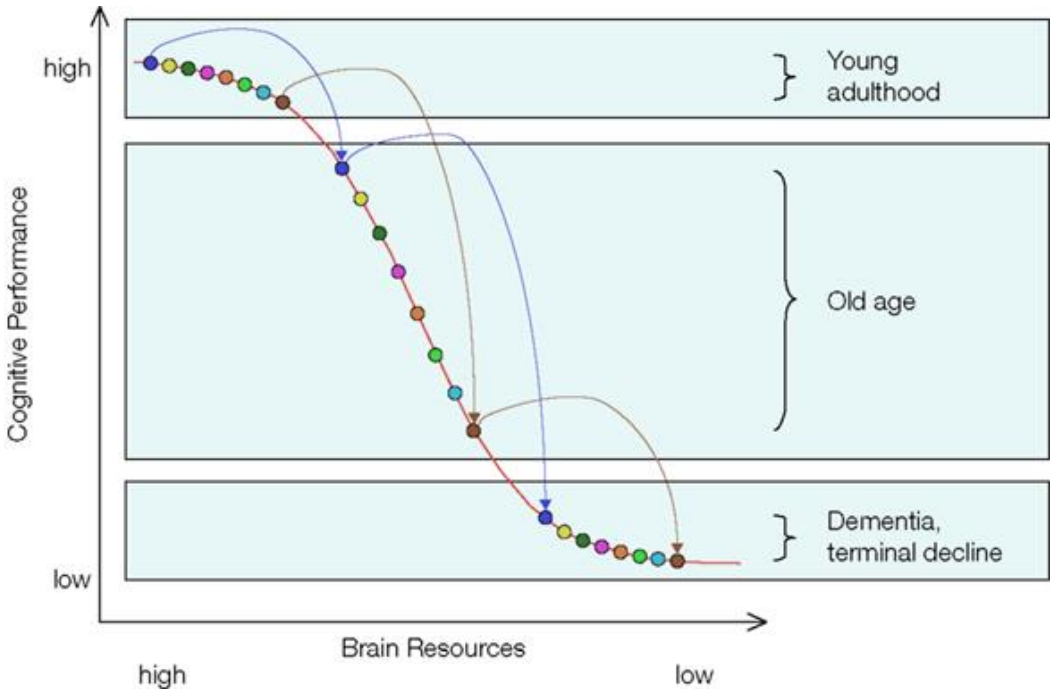

Figure 3. The resource-modulation hypothesis posits that the relation between cognitive performance and brain resources is non-linear. The colored circles represent individuals with different brain resource, which can partly reflect his or her genetic predisposition. In old age, individual differences in brain resources may translate into increasingly larger individual differences in cognitive performance. When brain resources are depleted, such as in dementia, the difference in cognition is reduced again. Adapted from Lindenberger et al. (2008)

In the following sections, I will summarize behavioral and neuroimaging findings of three extensively investigated DA-related genetic polymorphisms, and illustrate the interaction between age and candidate genes on cognitive and neural integrity by comparing research findings from younger and older adults. Incorporating genetic data in cognitive neuroscience and cognitive aging research are motivated by several factors. First, given the well-established molecular functions of the candidate genes, this approach might help understand the molecular and biological mechanisms of cognitive phenotypes in the general population. For example, in the present thesis, we focused one three genetic polymorphisms, *DRD2/ANKK1*-Taq1A, *DRD2*-C957T, and *COMT*-Val158Met, all of which have been associated with DA functioning in PFC or caudate. Linking DA-related genes to WM-related behavioral and imaging data, allows us to evaluate the influence of DA on WM functioning, and characterize WM mechanisms at the molecular level. Second, because of the magnified genetic influence in older adults observed in many previous studies, the aging population may be more sensitive to genetic effects on behavioral and imaging phenotypes than younger adults. Moreover, since genetic effects may be greater on brain-based intermediate phenotypes than for behavior, the genomic imaging studies should be especially suitable for investigating the neurobiological mechanisms of cognitive and brain aging. Third, as illustrated in Figure 2, despite a remarkably negative age trend for cognition, performance is well preserved in some older adults, even comparable to that of younger adults. The neural mechanisms behind successful cognitive aging and brain maintenance in late life could be investigated by conducting cognitive-

neurogenetic studies in older adults. This question is beyond the scope of the current thesis, but has been addressed in other work (Nyberg et al., 2015).

DRD2/ANKK1-Taq1A (rs1800497)

The DA D2 receptor is encoded by the *DRD2* gene. The Taq1A polymorphism (rs1800497) is located about 10 kb downstream from the *DRD2* gene, and lies within the *ANKK1* gene. Individuals who carry the A allele have reduced D2 receptor density in the caudate and putamen compared to non-carriers (Jönsson et al., 1999; Pohjalainen et al., 1998; Thompson et al., 1997). The presence of an A allele has been related to worse performance on executive function tasks (Berryhill et al., 2013; Jocham et al., 2009; Persson et al., 2015). However, some studies have found no such effects (Cerasa et al., 2009), or even a reversed effect (Bartres-Faz et al., 2002; Richter et al., 2017; Tsai et al., 2002) of the Taq1A polymorphism on cognition. Thus, the association between the *DRD2* gene and behavioral performance remains unclear.

Although the influence of *DRD2/ANKK1*-Taq1A on brain and cognition in healthy aging has received less attention, there is some evidence suggesting that this genetic polymorphism might modulate striatal function. For example, an fMRI study demonstrated that A carriers had worse cognitive performance than non-carriers of this allele in a memory updating task, along with lower caudate BOLD signal during updating, and this genetic influence was only observed in older adults, demonstrating a magnified genetic effect in aging (Persson et al., 2015). In line with previous work, a positive correlation between caudate BOLD signal and WM updating performance was found, suggesting an important role of caudate during WM updating. However, this association was only significant in A non-carriers, indicating that A carriers might have difficulty in modulating caudate activity during memory updating (Persson et al., 2015). The effect of the Taq1A polymorphism on brain structure, such as GM volume or white-matter integrity, was previously not known and therefore addressed in studies I-III of the current thesis. We investigated the influence of Taq1A polymorphism on GM volume in study I and study II, and the effects on white-matter integrity in study III. We also evaluated the additive effects of this polymorphism and *DRD2*-C957T on WM-related brain function, which will be elaborated below.

DRD2-C957T (rs6277)

The C957T polymorphism is a mutation located within the 957th base pair of the *DRD2* gene. In vivo PET studies in humans have found that the presence of the T allele of the C957T polymorphism is associated with higher striatal DA D2 binding potential (Hirvonen et al., 2004, 2009a; Smith et al., 2017), and the C allele has been associated with higher DA binding potential in cortex and thalamus (Hirvonen et al., 2009b) .

The *DRD2*-C957T polymorphism has been found to influence a wide range of cognitive functions, although the results regarding the direction of the genetic effect are mixed. For example, the T allele has been associated with better performance in tasks assessing updating (Rodriguez-Jimenez et al., 2007), WM maintenance (Xu et al., 2007), executive functions

(Klaus et al., 2017), rule-based category learning (Byrne et al., 2016), and general cognitive ability (Bolton et al., 2010). Conversely, it has been found that C carriers have faster learning rates in a motor task (Huertas et al., 2012), more efficient inhibition ability and larger attentional blink size (Colzato et al., 2013), which is an index of the amount of attentional resources. For episodic memory, C homozygotes showed better familiarity-based recognition (Richter et al., 2017), and better recollection-based recall (Li et al., 2013). Among older adults, C carriers show better episodic recall (Li et al., 2013) and were more efficient in inhibiting unwanted action tendencies in a stop-signal task (Colzato et al., 2013). Consistent with the resource-modulation hypothesis, these effects were stronger in older than in younger adults (Colzato et al., 2013; Li et al., 2013).

The lack of consistency regarding genetic effects on cognition is not surprising, because cognitive functioning is influenced by complex interactions among a variety of factors, such as genetic and environmental factors, strategies, personalities, and mood factors. The effect size for single genes is small, and can only account for a small amount of the variance of cognitive performance in younger adults. Another explanation for these inconsistencies might be that the two functionally opposing components that are important for WM, cognitive stability and flexibility, may be differently influenced by DA functioning in PFC and striatum (Cools and D'Esposito, 2011). The C allele of *DRD2*-C957T polymorphism has been associated with increased DA receptor binding in PFC. Thus, it is likely that C carriers perform better in maintaining stable representations. On the contrary, the T allele is related to increased DA receptor binding in striatum, T carriers might, therefore, perform better in tasks requiring flexible updating of information in response to task requirements. As a result, the direction of the genetic effects of the C957T polymorphism on cognition may depend on the balance between stability and flexibility required by the tasks.

The findings concerning the effects of C957T on brain structure and function are mixed. For example, a structural MRI study showed that carriers of the C allele together with the T allele of *CHRNA4* gene, which affect cholinergic neurotransmission on DA signaling, had smaller caudate volumes (Markett et al., 2013). Ascending dopaminergic pathways that project from the VTA in the midbrain to the PFC via the basal ganglia has been related to a gating function by allowing behaviorally relevant information to enter into WM (O'Reilly, 2006). The results of Markett et al. (2013) revealed that dopaminergic function might influence brain volume in caudate, a key region within the DA pathway. If smaller brain volume reveals brain tissue or neuron reduction, the C allele might be relatively detrimental compared to the T allele in this study. However, without observing genetic effects on cognition, it is hard to infer whether the C allele is beneficial or not. On the other hand, an fMRI study, which investigated the association between C957T and brain activity during an incentive delay task revealed that the C allele might be beneficial. The results demonstrated better recognition performance and greater brain activity in striatum and hippocampus in C957T – C carriers compared to T carriers (Richter et al., 2017). As the C allele is associated with lower striatal DA, but higher extra-striatal DA, these results might reflect that extrastriatal DA is important for encoding and retrieval of reward-associated information. An alternative explanation is that higher baseline

DA levels in caudate, such as in T carriers, are linked to a detrimental, rather than beneficial, effect of reward on attentional performance (Richter et al., 2017). A DTI study also found stronger structural connectivity, as indexed by FA, in white matter tracts between basal ganglia and frontal regions in C carriers compared to T carriers (Markett et al., 2017). This study suggested that DA might influence white-matter integrity of the connection between two target regions in the DA pathway.

Since the C allele has been associated with more extrastriatal DA (Hirvonen et al., 2009b) and the T allele has been associated with more striatal DA (Hirvonen et al., 2004, 2009a; Smith et al., 2017), the controversial findings mentioned above might reflect differential roles of PFC DA and striatal DA on brain function in PFC and striatum, and on WM stability and flexibility (Cools and D'Esposito, 2011). There is a general lack of knowledge about the effect of DA-related genes on neurocognition, and in particular how such effects may interact with age. In study II of the thesis, we conducted an fMRI study in a large sample across a wide age range. Here, we examined how age and two *DRD2* polymorphisms (C957T and Taq1A) affected both in-scanner and offline WM performance and WM-related brain activity. In study III, we also tested whether C957T influences white-matter integrity.

Catechol-O-methyltransferase (*COMT*) Val158Met (rs4680)

The COMT enzyme is involved in extracellular degradation of synaptically released DA in the PFC (Matsumoto et al., 2003; Tunbridge et al., 2007, 2006). Val158Met polymorphism in the gene encoding COMT modulates DA transmission in PFC. Val homozygotes have three to four times higher turnover rates than Met homozygotes (e.g., Lotta et al., 1995), resulting in lower prefrontal DA availability, and less efficient PFC functioning.

In younger adults, a number of studies have demonstrated that Val carriers have worse cognitive performance in tasks of executive control, episodic memory, reasoning, as well as in tasks probing anxiety and emotional state (for a review, see Witte and Flöel, 2012). However, other studies have failed to find effects of *COMT* on the n-back WM task (Blanchard et al., 2011) or a WM updating task (Stuart et al., 2014). These mixed observations could be explained by small effect sizes of single genes on cognition in younger adults. Two meta-analyses have shown that the *COMT* gene was only weakly associated with cognitive performance (Barnett et al., 2008, 2007). Neuroimaging studies have shown that higher WM performance in Met carriers was associated with less PFC activity, indicating more efficient PFC function during WM tasks (Egan et al., 2001; Sambataro et al., 2009).

Findings are more consistent concerning the association between *COMT* and cognition in older adults. For example, Met carriers had better performance on WM updating and maintenance than Val carriers (Nagel, 2008). The Met allele has also been associated with higher executive function and fluid intelligence (de Frias et al., 2005). In addition, the *COMT* polymorphism may modulate the association between working and episodic memory (Papenberg et al., 2014a). Longitudinal studies have also shown that Val carriers demonstrate significant decline in executive function over a 5-year period, whereas Met carriers' performance remained stable

(de Frias et al., 2005). Further, age-comparative studies have reported that the effect of the *COMT* gene on cognition was magnified in older adults (de Frias et al., 2005; Papenberg et al., 2014a), and in participants with low cognitive resources (Papenberg et al., 2014a).

Responsivity of the WM network to changing task demands is critical to successful task performance. Consistent with this notion, age-invariant performance is often demonstrated in WM tasks when load is low, and older adults often show over-recruitment of DLPFC compared to younger adults. Conversely, when WM load increases, older adults often recruit DLPFC to a lesser extent, and show worse WM performance than younger adults (Cappell et al., 2010; Nyberg et al., 2015). These findings suggest that PFC function is less efficient in older adults. A neurogenetic study by Nyberg and colleagues (2015) demonstrated similar brain activity patterns in younger *COMT* Val carriers as in older adults. Using a WM updating task, they found that older adults and younger Val carriers had higher DLPFC activation during a less demanding WM condition. In contrast, during a more demanding WM condition, both older adults and younger Val carriers showed less activation in DLPFC compared with younger adults and older Met carriers. There was no difference in WM performance across age and genetic groups (Nyberg et al., 2015), demonstrating that brain parameters may be more sensitive than cognitive measures in disclosing genetic effects. Another fMRI study revealed that WM-related fronto-parietal network connectivity was modulated by *COMT*, with Val homozygotes showing increased PFC-related connectivity to other nodes in this network compared to Met homozygotes. Again, no genetic difference was observed in WM performance (Sambataro et al., 2009). These results indicate less cortical efficiency in Val carriers compared to Met carriers. In addition, consistent with the resource-modulation hypothesis, larger *COMT*–related differences were seen in older than in younger adults, indicating a magnified genetic effect in aging (Sambataro et al., 2009). These two findings may reflect that *COMT* can modulate DLPFC efficiency, with Val carriers being less efficient.

To our knowledge, only one DTI study has investigated the influence of *COMT* on white-matter integrity (Papenberg et al., 2015b). These investigators found that Val carriers had reduced white-matter microstructure in several PFC white-matter tracts compared to Met carriers, and this effect was only found in the oldest age group (81-87 years old), and not in two younger groups (60-66 years old and 70-78 years old; Papenberg et al., 2015b). We replicated this particular analysis in study III using a voxel-wise approach, and in study IV we further explored whether *COMT* modulates longitudinal changes in white-matter integrity.

Gene-gene interactions

Cognition is a polygenic trait, and the structure and function of certain brain networks are modulated by complex interactions among many polymorphisms. The additive effect sizes of several genes that have similar molecular functions might be larger than that of any individual gene. Previous behavioral studies in younger adults have demonstrated additive cognitive effects of DA-related genes, such as the *COMT* and the *DRD2*/*ANKK1* gene (Taq1A) (Wishart et al., 2011), the *DRD2* (C957T) and the DAT gene (SLC6A3) (Li et al., 2013), the *DRD2* (C957T) and the CHRNA4 (rs1044396) (Markett et al., 2011), as well as different

polymorphisms within the *DRD2* gene (Taq1A and C957T; Bolton et al., 2010). Gene-gene interactions on cognition have been more pronounced in older than in younger adults. For example, in a study investigating the interaction of three DA-related genes (*DRD2*-C957T, *DAT1*-SLC6A3 and *DRD3*-Ser9Gly), older adults carrying two or three genotypes associated with higher DA signaling had better pictorial memory than older individuals carrying only one or no beneficial genotypes. No such genetic effects were found in younger adults (Papenberg et al., 2013). Greenwood et al. (2014) found significant interactions between the *COMT*-Val158Met and the *DBH*-1021C/T (a polymorphism in the gene encoding DA beta-hydroxylase) on WM among older people, but not in midlife (Greenwood et al., 2014). Combined genetic effects of the *DRD2* gene (C957T) and the *DAT* gene (SLC6A3) on episodic memory have also been observed (Li et al., 2013), and were stronger in older than younger adults. Further, a reliable interaction between DA (*DRD2* - C957T) and glutamate receptor genes (NR3A - Val362Met) on episodic memory was observed in older adults only (Papenberg et al., 2014b). Combined genetic effects of the *DRD2* (C957T) and the CHRNA4 (rs1044396) genes were also observed on striatal volume (Markett et al., 2013). In study II, we examined the joint effects of two *DRD2* polymorphisms, C957T and Taq1A on WM and brain function in both younger and older adults. Both *DRD2*/C957T and *DRD2/ANKK1*-Taq1A have been associated with DA D2 receptor density in PFC/striatum, and the two genetic polymorphisms can be combined to examine how they contribute to the effects of DA-related genes on WM functioning.

AIMS

The aim of this thesis is to contribute to the understanding of mechanisms underlying age-related differences and changes in WM at both neural and genetic levels. The approach was to investigate the effects of age and DA-related genes on behavior, especially WM performance, brain structure, and WM-related brain function. We focus on three DA-related genetic polymorphisms, *DRD2*/*ANKK1*-Taq1A, *DRD2*-C957T, and *COMT*-Val158Met. The specific aims of the four individual studies are summarized below.

Study 1 examined the influence of *DRD2*/*ANKK1*-Taq1A on GM volume in striatum in a group of older adults, and explored how the genetic effect interact with age.

Study 2 investigated (1) age effects on brain activity in striatum during WM; (2) single and additive effects of the *DRD2*-C957T and *DRD2/ANKK1*-Taq1A polymorphisms on WM performance and WM-related brain activity; and (3) whether these genetic effects were magnified in aging.

Study 3 explored (1) the association between white-matter integrity and WM performance; (2) whether white-matter integrity can account for the age differences in WM; and (3) whether the three DA-related genes affect white-matter integrity.

Study 4 focused on (1) age-related changes in white-matter integrity across 5-10 years; (2) age trajectories of white-matter integrity across the adult life span combining longitudinal and cross-sectional data; (3) whether longitudinal changes in white-matter integrity can account for changes in cognition, especially WM and processing speed; and (4) whether *COMT* affects longitudinal changes in white-matter integrity.

MATERIALS AND METHODS

Below, I will summarize the study samples and the cognitive tasks used in the individual studies. Participants' demographic information for the four studies is summarized in Table1. Then I will briefly introduce the neuroimaging analyses used, including VBM (study I), fMRI (study II) and DTI (study III and IV), along with the procedures for genotyping.

The SNAC-K project

Study I was carried out using data from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) project, a longitudinal population-based study. To date, the project consists of a baseline and 5 follow-up test occasions. Only the baseline data were used in study I. 4590 persons who were ≥ 60 years old and lived on the island of Kungsholmen in central Stockholm were randomly selected by age stratification (60, 66, 72, 78, 81, 84, 87, 90, and 90+ years). 3363 persons who accepted to participate underwent medical examinations and interviews. Within this sample, a randomly selected subsample of 556 individuals, who fulfilled the initial inclusion criteria (e.g., non-institutionalized, nondisabled, no metal implant in their body) underwent assessment with structural MRI. Participants were excluded if they had a dementia diagnosis at baseline, or at either of the two follow-ups (after 3 and 6 years), schizophrenia, bipolar disorder, self-reported stroke, stroke observed on the MR images, self-reported Parkinson's disease, or self-reported epilepsy. In study I, data from 27 participants were excluded from analysis due to missing genetic data. 8 participants older than 90 years were excluded, as they might represent a positively selected subgroup relative to the rest of the study sample. The final MRI sample consisted of 387 participants (age range = 60–87 years; mean age = 69.3 years).

The Betula project

Study samples used in studies II, III and IV of the thesis were selected from the longitudinal, population-based study Betula (Nilsson et al., 2004, 1997). Betula aims to explore the development of memory functioning and health across the adult life span, especially in old age. Participants were randomly selected from the population registry in Umeå, Sweden using an age-homogeneous, narrow age cohort (NAC) design. A NAC design requires that participants for each age cohort were tested at a constant age (i.e. all participants were 35, 40, 45, 50, 55, 60, 65, 70, 75, and 80 years of age at baseline.). Genetic, demographic, and MMSE data across samples are presented in Table 1.

Table 1. Background information

	Study 1 SNAC-K		Study 2 Betula - T5		Study 3/4 Betula - T5	Study 4 Betula - T6	Study 4: Betula - T7
	Younger	**Older**	**Younger**	**Older**	**Whole sample**	**Whole sample**	**Whole sample**
N	220	167	191	112	327	198	91
Taq1A (A+/A-)	69/151	57/110	70/121	37/75	107/198	—	—
C957T (CC/CT/TT)	—	—	60/100/31	34/58/20	93/167/54	—	—
COMT (ValVal/Any Met)	—	—	—	—	69/245	44/146	19/69
Age, years	62.8 (60-66)	77.8 (72-87)	53.5 (25-65)	73.4 (70-80)	61.3 (25-80)	64.4 (30-85)	74.2(65-90)
Gender (f/m)	128/92	103/64	100/91	66/46	174/153	93/105	42/49
Education, years	13.9 (7-28)	11.6 (5-25)	14.3 (7-26)	10.8 (6-26)	12.9 (6-26)	13.3(6-26)	13.8(6-26)
MMSE	29.4 (25-30)	29 (25-30)	28.4 (24-30)	28 (24-30)	28.1 (24-30)	28.2 (24-30)	—

Recruitment started in 1988 and 7 waves of data collection with 5-year intervals have been completed. MRI data collection started at the fifth wave (T5) and here subjects were followed for 10 years (2 waves, T6 and T7). Study II and III used the baseline MRI sample (T5), and study IV used the MRI sample for all three time points (T5, T6, and T7).

In-scanner working memory task

The in-scanner WM task used in studies II and III involved a blocked design with 3 task conditions: manipulation, maintenance, and control (Figure 4). In the manipulation condition, two letters were presented for 2 sec each. Participants were asked to generate the subsequent letters of these two letters according to the alphabetical sequence, and to keep those in memory (target letters). After a fixation star, which was presented for 3.5 sec, participants were presented with a probe letter and asked to decide whether the probe letter matched any of the two target letters. In the maintenance condition, participants were presented with four target letters. After the fixation star disappeared, they needed to decide whether the probe letter was the same as any of the four target letters. The control condition was similar to the maintenance condition, but here the target letters were all identical. Behavioral data from this WM task, and accompanying task-related brain activity were analyzed in Study II, and the behavioral data were also analyzed in relation to the DTI data in study III.

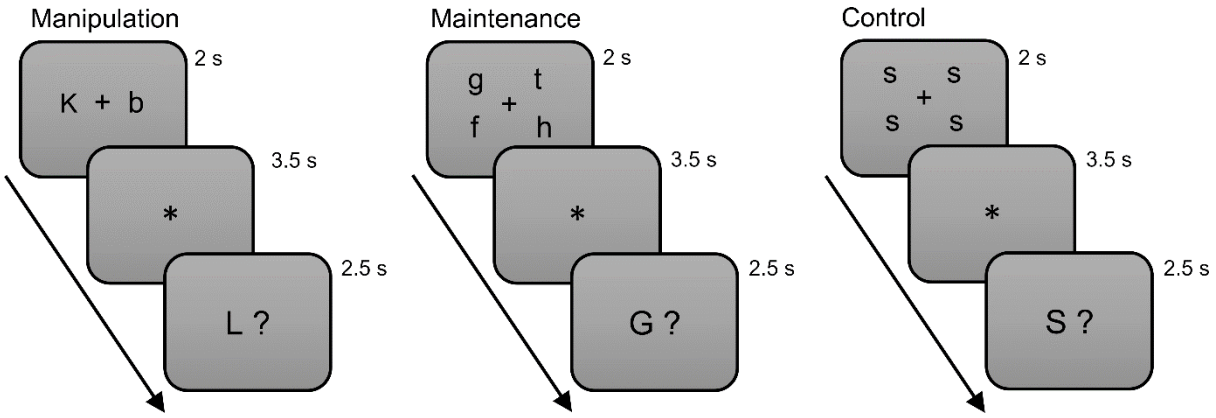

Figure 4. Illustration of the in-scanner WM task

Off-line cognitive assessments

In addition to the in-scanner WM task, participants in both SNAC-K and Betula underwent a battery of tests covering a wide range of cognitive domains. I will briefly describe the task paradigms below. Composite scores were used when the cognition was measured by more than one cognitive tasks.

Processing speed

In SNAC-K, the measure of perceptual speed consisted of composite scores from two tasks: digit cancellation (Zazzo 1974) and pattern comparison (Salthouse and Babcock 1991). In digit cancellation, participants were instructed to sequentially cross out the digit "4" in 11 rows of random digits. In pattern comparison, participants were instructed to determine whether pairs of abstract line figures were similar or not as soon as possible.

In Betula, the estimate of perceptual speed consisted of composite scores from three tasks: letter-digit substitution, letter comparison, and pattern comparison (Salthouse and Babcock 1991). For letter-digit substitution, a paper with a letter-digit transformation key on the top was shown to the participants. They were required to write down the paired digit for each letter according to the transformation key. The letter comparison task involved determining whether pairs of non-word strings of 3–9 letters were similar or not. The pattern comparison task was the same as in SNAC-K.

Episodic memory

In SNAC-K, episodic memory involved free recall and recognition. Participants were instructed to memorize 16 unrelated concrete nouns. Immediately after presentation, they were asked to recall the words. Then participants were given a self-paced recognition task that included 16 targets and the same number of lures. Participants were also asked to distinguish whether they could recollect the word or if the word was merely familiar. The scores were based only on recollection responses.

In Betula, episodic memory was measured using five episodic memory tests (e.g., Gorbach et al., 2017; Pudas et al., 2014): (1) participants were asked to enact commands according to short sentences provided by the tester, and then to immediately recall the commands orally; (2) The task was to learn the commands visually and verbally without enactment and recall immediately; (3 & 4) After a short delay, participants were asked to recall nouns from the sentences described earlier with noun categories (e.g., fruits, animals) as cues; (5) a series of common unrelated nouns were presented auditorily, and participants were asked to recall immediately after presentation.

Semantic memory/general knowledge

Semantic memory tasks consist of vocabulary and general knowledge tests, which were included in both Betula and SNAC-K. For vocabulary (Dureman, 1960), participants were instructed to choose words representing synonyms to each target word among five words. The general knowledge task consisted of 10 questions (e.g. "What is the capital of Uruguay?") that have been found to be moderately difficult for older people (Dahl et al., 2009). Participants needed to select the correct answer out of two alternatives.

Verbal fluency

In SNAC-K, verbal fluency was measured using letter fluency and category fluency. Letter fluency included two tasks, in which participants were asked to generate words beginning with the letters F and A, respectively. Category fluency Included two tasks, in which participants were asked to generate words belonging to the categories of animals and professions.

In Betula, participants were asked to generate as many words as possible according to the following instructions: (1) words beginning with the letter A, (2) words with five letters beginning with the letter M, and (3) professions starting with the letter B.

Fluid intelligence

Fluid intelligence was only included in Betula and was measured using the block design task (maximum = 51; Wechsler, 1981). Block design is a visuospatial problem-solving task. This test is a subtest of the Wechsler Adult Intelligence Scales-Revised, and has a high correlation with full scale IQ from WAIS-IV (r=0.66; Groth-Marnat and Wright, 2016). Participants were asked to recreate spatial patterns using colored blocks shown to them on cards.

Working memory

The off-line WM task was only included in Betula, and was measured using the 2-back task. In this task, participants were orally presented with a sequence of words and needed to judge whether the current word was the same as that was heard two words earlier.

Genotyping

Blood samples were collected for DNA extraction for all the participants. In SNAC-K, genotyping of candidate genes was performed using MALDI-TOF analysis on the Sequenom MassARRAY platform at the Mutation Analysis Facility, Karolinska Institutet. Data quality control was performed and single nucleotide polymorphism (SNP) call rate for *DRD2/ANKK1* – Taq1A (rs1800497) was over 95%. The genotyping results did not deviate from Hardy-Weinberg Equilibrium ($p > 0.01$). In Betula, a total of 52 SNPs, including *DRD2/ANKK1* – Taq1A (rs1800497), *DRD2* – C957T (rs6277) and *COMT* (rs4680) were genotyped using the Sequenom iPLEX gold assay and MassARRAY MALDI-TOF mass spectrometry platform. Each SNP had a call rate over 95% and was in Hardy Weinberg equilibrium ($p>0.001$).

Brain imaging analysis

Grey-matter volume

We used voxel-based morphometry (VBM) to analyze GM volume data in study I and II. T1-weighted images were preprocessed using SPM12 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/). First, images were segmented

into GM, white matter, and cerebrospinal fluid using the unified segmentation approach (Ashburner and Friston, 2005). Then Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL; Ashburner, 2007), a fast and accurate algorithm for alignment and normalization, was used to process GM images. The average GM template for all subjects was generated iteratively, and used to calculate the parameters of the non-linear transformation (subject-specific flow-field images) from itself to each individual image. Then the template was affine transformed into standard Montreal Neurological Institute (MNI) standard space. The transformation parameters were combined with each individual's flow-field images to bring each individual's image into MNI space. In order to increase the signal-to noise ratio, images were smoothed with a full-width at half maximum Gaussian kernel of 9 mm in three directions. After this step, all images were spatially aligned in MNI space.

Since we had prior hypotheses regarding DA-related genetic effects on caudate or DLPFC, we used a region-of-interest (ROI) approach instead of a voxel-wise approach to analyze the preprocessed data. Volumes of bilateral caudate (Study I and II) and DLPFC, including Brodmann area 8 and 9 (Study II) were extracted using masks defined by the Automated Anatomical Labeling atlas, and the Brodmann anatomical template implemented in the WFU_pickatlas. The size of the intracranial volume (ICV) provides a large portion of brain volume variability that influence regional volume and was therefore partialled out by adjusting regional volumetric data using the covariance approach (Jack et al., 1989; Raz et al., 2005): adjusted volume = raw volume − b (ICV−mean ICV), where b is the slope of regression of volume on ICV.

Functional MRI

fMRI data analysis was used in Study II. All fMRI data were preprocessed using SPM12. An in-house developed software (DataZ) was used for batching and visualization of statistical maps. Before analysis, the data were preprocessed in the following way: slice timing correction, movement correction by unwarping and realignment to the first image of each volume, normalization to a sample specific template using DARTEL (Ashburner, 2007) and affine alignment to MNI space and smoothing with an 8-mm FWHM Gaussian kernel. The final voxel size was 2 × 2 × 2 mm.

Preprocessed fMRI images were further analyzed at two levels. The first-level analysis was carried out separately for each individual. General linear model (GLM) was fitted for each voxel to estimate the regressors for each condition. The manipulation > maintenance contrast for each participant was then entered into a group-level analysis. In the second-level group analysis, we conducted a 2 (age) × 2 (gene) analysis of variance (ANOVA) to investigate main effects of age and genetic polymorphism, and their interaction for each voxel. T-value statistical maps for the contrasts of these effects were then generated. We used two-step cluster-level inference to thresholding the statistical map. First, an uncorrected $p < .005$, with a 10-voxel extent threshold, as recommended by Lieberman et al. (2009), for the whole brain was used to define the clusters.

The retained supra-threshold clusters were small-volume corrected using a 6 mm radius sphere around the peak coordinates of caudate and DLPFC. Results that survived a cluster-level family-wise error (FWE) corrected threshold of $p < .05$ were considered as significant.

Diffusion tensor imaging

In the Betula study, DTI data were collected at both baseline (T5) and two follow-up occasions (T6 and T7). The baseline DTI data (T5) were used in study III, and longitudinal data (T5, T6 and T7) were included in study IV. Diffusion-weighted data were analyzed using the University of Oxford's Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) package (http://www.fmrib.ox.ac.uk/fsl). At baseline, three sessions of the subject-specific diffusion acquisitions were concatenated into a 4D file for each subject. Then the raw images were corrected for eddy-current induced distortions, and head movement by full affine aligning to the first non-diffusion weighted image (b=0). The transformation matrix was then used to rotate bval and bves files (Jenkinson and Smith, 2001). A binary brain mask was then generated using the first non-diffusion weighted image with the Brain Extraction Tool (BET) to exclude non-brain voxels. Finally, the preprocessed diffusion-weighted images were fitted to the DTI model. The tensor matrix with information in three directions (eigenvalues) were obtained for each voxel within the brain mask. Voxel-wise maps of FA, MD, AD, and RD were generated using the three eigenvalues. Since there was only one session of DTI scanning at T7, we only included the first session of T5 and T6 in the longitudinal analysis in study IV for consistency. All other preprocessing steps were the same as those used for the baseline DTI data.

TBSS

Tract-based spatial statistics (TBSS) was used to align and skeletonize the FA/MD images for further group analysis. First, FA images were non-linearly transformed to MNI space using the high-resolution standardized image (FMRIB158_FA) as a target. All transformed FA images were merged into a single 4D image, and a mean image was created by averaging all FA images. The mean FA image was fed into the tract-skeleton generation program to produce a white-matter tract skeleton, which represents the white-matter tracts common to all subjects. Then, a binary skeleton mask was generated by thresholding the mean FA skeleton image with FA values larger than 0.2. Finally, each subject's FA image was projected onto the group skeleton mask. MD/AD/RD images were processed using a similar method as for FA images.

Statistical analysis – voxel-wise approach

The group analysis was conducted using both a voxel-wise and an ROI approach. For the voxel-wise analysis, the Randomise tool (part of FSL), and the Permutation Analysis of Linear Models (PALM) tool (Winkler et al., 2014) were used. PALM is especially suitable for analyzing repeated measures data with more than two time points. The analysis steps were similar for both Randomise and PALM, with only minor differences, as described below. First, GLMs were fitted to white-matter skeletonized images, and the regression coefficients for each voxel were

estimated to generate t-statistic maps. Threshold-free cluster enhancement (TFCE) was then applied on the t-maps. Since the null distribution of TFCE-enhanced statistical maps was unknown, a non-parametric permutation test with 5000 permutations was used to generate the null distribution, and to calculate corrected p-values for each voxel. In PALM, exchangeability blocks are especially needed to specify the permutations to be done within and between subjects/groups. For example, some subjects had DTI data with 2 time points and others had 3 time-points, thus permutation needs to be done within each subject first, but not for all data of all subjects. Then, in Randomise, the corrected-p maps were Bonferroni corrected if more than one test was conducted. In PALM, multiple comparison correction is done automatically using FWER-correction. An adjusted-p value of less than 0.05 was considered statistically significant.

Statistical analysis – ROI approach

We extracted mean FA/MD/AD/RD across the entire skeleton, and for seven major tracts, including corpus callosum (genu, body and splenium), external capsule, internal capsule, cingulate gyrus, superior longitudinal fasciculus, corona radiata and posterior thalamic radiation. The extraction was done using the JHU-ICBM-DTI-81 white-matter atlas, implemented in FSL, as the template. The extracted mean FA values were then imported into R for further statistical analyses.

Statistical analysis – Voxel-wise mediation

Mediation analyses were conducted at each voxel in study III to investigate whether, and in which brain regions, white-matter FA can mediate age-related differences in WM. A Sobel test was used to calculate the standardized mediation effect for each voxel. In equation 1, *a* and *b* denote the coefficients of the two paths (from age to white matter and from white matter to WM) and *Sa* and *Sb* are the standard deviations of the paths. Sex was regressed out for both independent (age) and dependent (WM) variables, and for the FA values of all the voxels. Sobel z values were calculated for each voxel using equation 1. TFCE was applied on the z-map and 5000 permutations were conducted on the TFCE-enhanced z-maps. The voxel-wise mediation analysis was conducted using the TFCE-mediation package (Lett et al., 2017) in Python.

$$Zvalue = \frac{a \times b}{\sqrt{b^2 \times S_a^2 + a^2 \times S_b^2 + S_a^2 \times S_b^2}} \quad (1)$$

Generalized additive mixed model

In study IV, generalized additive mixed model (GAMM) was used to characterize non-linear age trajectories of white-matter integrity across the adult life span. GAMM extends the generalized linear mixed mode by including an assumption-free “smooth” function of the predictors. The

smooth function is estimated as linear combinations of spline basis terms, which find the optimal relations between the predictor and outcome (Jones and Almond, 1992). GAMM and GAM packages in R were used to carry out the analyses. The model is shown in Equation (2). The models are fitted for each ROI separately.

$$Y_i = S(age) + Sex + b_0 + b_i + e \quad (2)$$

In the model, the dependent variable is the mean FA in one ROI for the individual i. *S(age)* represents the smooth (non-parameter) function of age. *Sex* is the covariate. Both age and sex are fixed effects. b_i is the random intercept for each subject and b_0 is the mean intercept across the whole sample.

INDIVIDUAL STUDIES

Study I

Influence of the *DRD2/ANKK1* Taq1A polymorphism on caudate volume in older adults without dementia

Xin Li, Goran Papenberg, Grégoria Kalpouzos, Lars Bäckman, Jonas Persson

This study was published in 2018 in *Brain Structure and Function*

Background

DA plays a critical role in brain and cognitive integrity. The DA D2 receptor has the highest density in striatum and is sparsely distributed in neocortical and limbic regions (Camps et al., 1989; Hall et al., 1994). The DA D2 receptor is encoded by the *DRD2* gene, and DA D2 receptor density has been associated with caudate volume (Woodward et al., 2009). The Taq1A polymorphism (rs1800497) is located about 10kb downstream from the *DRD2* gene and lies within the *ANKK1* gene (Neville et al., 2004). The presence of the A allele of the Taq1A polymorphism has been associated with reduced D2 receptor density in striatum (Jönsson et al., 1999; Pohjalainen et al., 1998; Thompson et al., 1997). In this study, we examined the effects of the *DRD2/ANKK1*-Taq1A on caudate volume and how this effect may interact with age.

Methods

The whole sample was divided into two age groups: 60–66 years (younger old) and 72–87 years (older old), and two genetic groups: any A carriers and GG carriers. All participants underwent a battery of cognitive tests covering four domains including perceptual speed, episodic memory, semantic memory, and verbal fluency. The T1-weighted MR images were pre-processed through a pipeline consisting of segmentation, normalization, modulation and smoothing in SPM12. Volumes of left and right caudate were extracted. Analysis of covariance (ANCOVA) was conducted using SPSS to investigate the effect of age, *DRD2/ANKK1*-Taq1A and their interaction on caudate volumes and cognitive performance.

Results

A significant main effect of age was observed in the caudate nucleus, reflecting smaller volumes in the older than in the younger age group. Carriers of the A allele had smaller caudate volumes compared to noncarriers in relatively older adults, and this interaction was mainly driven by the right caudate. No genetic effect on caudate volume was observed in the younger age group. Cognitive performance was not affected by the polymorphism.

Conclusion

The results suggested a link between the DRD2 gene and caudate volume in older adults and extend previous observation of magnified genetic effects on cognition and brain function in old age to GM volume.

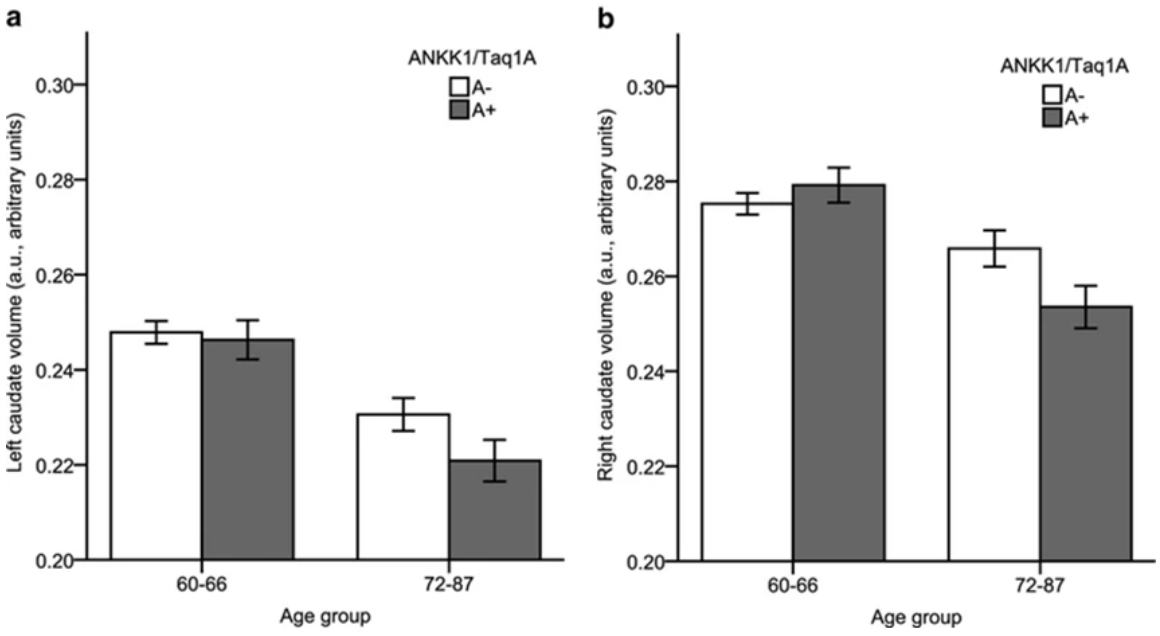

Figure 5. Left (a) and right (b) caudate volume for Taq1a any-A carriers (dark grey bars) and noncarriers (white bars) in two age groups. Error bars show standard errors of the mean.

Study II

The relationship of age and *DRD2* polymorphisms to frontostriatal brain activity and working memory performance

Xin Li, Lars Bäckman, Jonas Persson

This study was published in 2019 in *Neurobiology of Aging.*

Background

Healthy aging has been associated with WM decline. The neural mechanisms of age-related WM impairment have commonly been attributed to changes in PFC function (e.g., Madden et al., 2004b; Nyberg et al., 2015; Rieckmann et al., 2017). The striatum, and in particular the caudate, is also critical for WM (e.g., Lewis et al., 2004; Madden et al., 2004b; O'Reilly and Frank, 2006). For example, the caudate is involved in a dynamic gating function that regulate "GO" signals to the PFC to trigger information updating (O'Reilly and Frank, 2006). No study has investigated how age influence caudate functioning during WM.

DA in PFC (Durstewitz et al., 2000; Roberts et al., 1994; Seamans et al., 1998) and caudate (Clatworthy et al., 2009; Collins et al., 2000; Floresco and Magyar, 2006; Haluk and Floresco,

2009) has been associated with WM and WM-related brain activity. Age-related changes in WM (Volkow et al., 1998a) and PFC activity (Bäckman et al., 2011) during WM have been linked to alterations in dopaminergic signaling in aging (Karrer et al., 2017).

The *DRD2*-C957T and *DRD2/ANKK1*-Taq1A polymorphisms have high linkage disequilibrium (Duan et al., 2003; Hill et al., 2008; Stelzel et al., 2009), and have been related to DA D2 receptor density in PFC and striatum. Specifically, the C957T - T allele has been associated with lower DA D2 receptor density in PFC (Hirvonen et al., 2009b), whereas the C allele of the C957T polymorphisms and the A allele of the Taq1A polymorphism have been related to lower striatal DA D2 receptor densities (Hirvonen et al., 2004, 2009a; Smith et al., 2017). The single and additive effects of these two polymorphisms on WM performance and WM-related brain activity remain unclear. This study investigated the effects of age and the two *DRD2* polymorphisms on WM and WM-related brain activity, and whether potential genetic effects were magnified in aging.

Methods

Participants were scanned while performing a WM task that included three conditions: manipulation (high WM demand), maintenance (intermediate WM demand) and control (low WM demand). We separated the whole sample into two age groups (25-65 years; 70 years +), as older adults at 70 + years of age showed significantly lower WM performance than the younger age groups. For the behavioral data, we conducted a 2 (gene) by 3 (condition) ANCOVA with age, sex and education as covariates for the two polymorphisms and their combination. For the brain imaging data, separate 2 (age) by 2 (gene) ANOVAs were conducted for each of the two polymorphisms and for their combination on the contrast between the manipulation and maintenance conditions. Single and additive effects of the two polymorphisms on caudate volume were also examined as a control analysis to test whether the association between volumetric differences and genetic variance contribute to the genetic effect on brain activation and cognition.

Results

Significant age by condition interactions in caudate activity revealed lower caudate activity during the high-WM condition in older compared to younger adults. Single-gene analyses showed that individuals who carry the C allele of C957T, which has been associated with higher PFC DA binding, demonstrated better performance and larger brain activation in PFC (Figure 6) in the highly demanding WM condition. Combined genetics analysis found that there was an additive genetic effect on off-line 2-back performance and on brain activation, with the T allele of C957T combined with the G allele of Taq1A had better behavioral performance and greater caudate activation (Figure 7). The genetic influence on brain activation was only found in older adults. Volumetric data analysis showed smaller caudate volume in older compared to younger adults. No genetic effects or any interaction between gene and age were found for brain volumes.

Conclusion

The findings indicate that older adults have lower modulation of striatal activity during the high-demand WM condition. The single and additive effects of the *DRD2* polymorphisms on WM performance and related brain function suggested that genotypes associated with higher DA signaling were associated with better WM performance, and greater brain activity. In addition, the fMRI findings indicate separate roles of the two alleles of the C957T polymorphism on prefrontal and striatal brain activity. The results of magnified genetic effect on brain activation in older adults are consistent with the resource-modulation hypothesis, which posits that genetic influences may be larger in individuals with depleted brain resource, such as older adults, and suggest an important role of DA in age-related changes in brain function during WM.

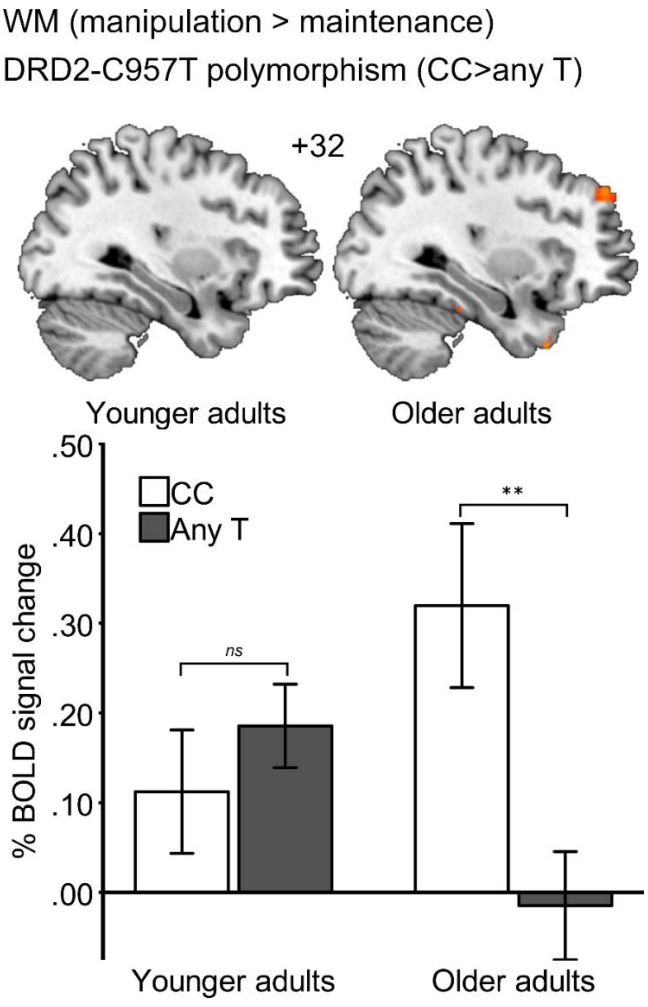

Figure 6. The effects of the *DRD2*-C957T polymorphism (CC > any T) in the younger and older age groups on brain activity in DLPFC during WM (manipulation–maintenance). Percent BOLD signal change is derived from the local maxima of right DLPFC (x y z = 32 48 38).

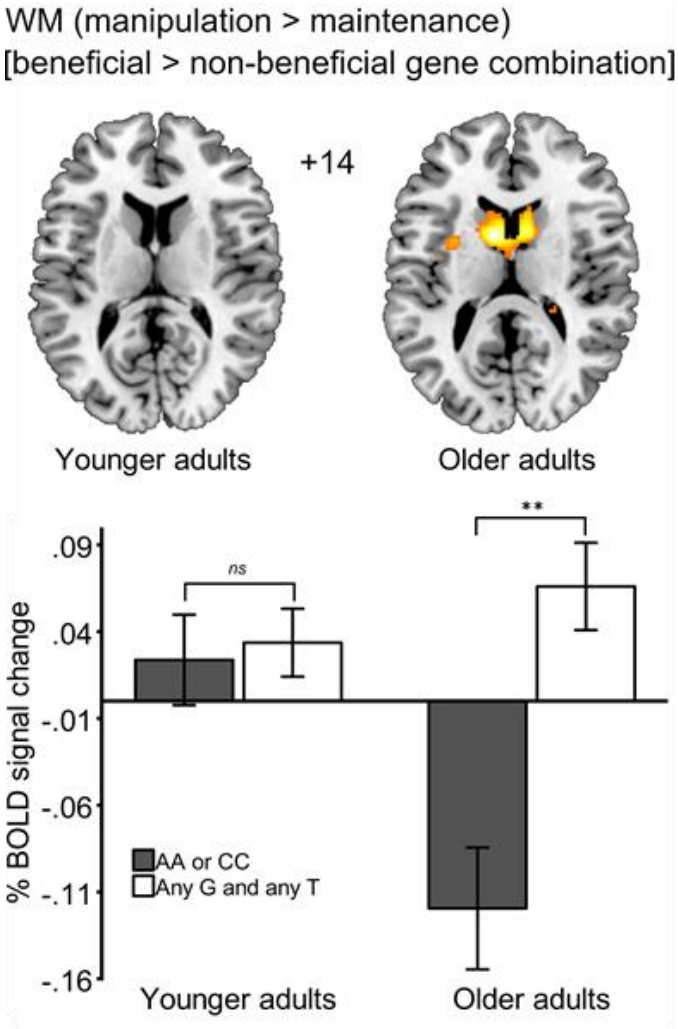

Figure 7. The additive effects of the two *DRD2* polymorphisms on striatal activity in younger and older age groups during WM (manipulation–maintenance). Percent BOLD signal change is derived from the local maxima of left caudate (x y z = -10 4 18).

Study III

White-matter integrity and working memory: Relationships to aging and dopamine-related genes

Xin Li, Alireza Salami, Lars Bäckman and Jonas Persson.

This study is in manuscript format.

Background

White matter refers to myelinated axons that are critical for inter-regional brain communication, and neural information transmission (Andrews-Hanna et al., 2007). WM, a crucial function underlying many higher-level cognitive processes, requires interaction and cooperation of multiple brain regions. Altered white-matter integrity (for reviews, see Bennett and Madden, 2014; Madden et al., 2012, 2009a) and WM performance (e.g., Charlton et al., 2010; Head et al., 2002; Kennedy and Raz, 2009a; Park et al., 2002) have been observed in

healthy aging. However, the associations between white-matter integrity and WM remain unclear and it is unknown which parts of the white matter that may account for the WM decline in aging. These questions will be addressed in this study.

DA has been associated with white-matter integrity (Rieckmann et al., 2016) and WM performance (e.g., Floresco and Magyar, 2006; Haluk and Floresco, 2009; Seamans et al., 1998). To our knowledge, there are only two previous studies that have investigated the influence of DA-related genes on white-matter integrity. Papenberg et al. (2015) found an effect of the *COMT* polymorphism on white-matter microstructure in the oldest age group (81–87 years), but not in younger age groups (60–66 and 72–78 years). *DRD2*-C957T has been associated with the white-matter tract connecting basal ganglia and frontal regions (Markett et al., 2017). This study examined the effects of three DA-related genes (*DRD2/ANKK1*-Taq1A, *DRD2*-C957T and *COMT*-Val158Met) on white-matter integrity.

Methods

We used TBSS to investigate the association between white-matter integrity and behavioral performance of a multiple-load WM task (Nyberg et al., 2014) across the adult life span in a sample of 327 participants (25-80 years). Mean FA was extracted for seven white-matter tracts, including corpus callosum (genu, body and splenium), external capsule, internal capsule, cingulate gyrus, superior longitudinal fasciculus, corona radiata and posterior thalamic radiation. We then compared the correlation coefficients of mean FA between different WM-load conditions using the Hotelling-Williams test. Using voxel-wise mediation analysis, we tested whether white-matter FA can mediate age-related differences in WM. Finally, the effects of DA-related genes on white matter-integrity were assessed by conducting 2 (gene group) × 2 (age group) ANCOVAs, with sex as covariate, for the three DA-related genetic polymorphisms.

Results

Results demonstrated associations between white-matter integrity and WM in multiple white-matter tracts, including corpus callosum, internal capsule, external capsule, corona radiata, posterior thalamic radiation, and superior longitudinal fasciculus. The associations were larger for the high WM-demand condition than for the low demand conditions, suggesting that the associations between white-matter integrity and WM may be load-dependent. In addition, white-matter integrity mediated the relation between age and WM, indicating that lower white-matter integrity might account for reduced WM performance in aging. There were weak effects of the *COMT* polymorphism on FA mainly in internal capsule, and these effects were driven by the older adults.

Conclusion

WM performance was associated with global white-matter integrity. Successful performance at higher WM demand might rely more on white-matter integrity than lower WM demand. Furthermore, age-related differences in white-matter integrity might partly accounted for the

age-related WM deficit. The genetic effect of the *COMT* Val158Met polymorphism on FA suggested a link between DA and white-matter integrity.

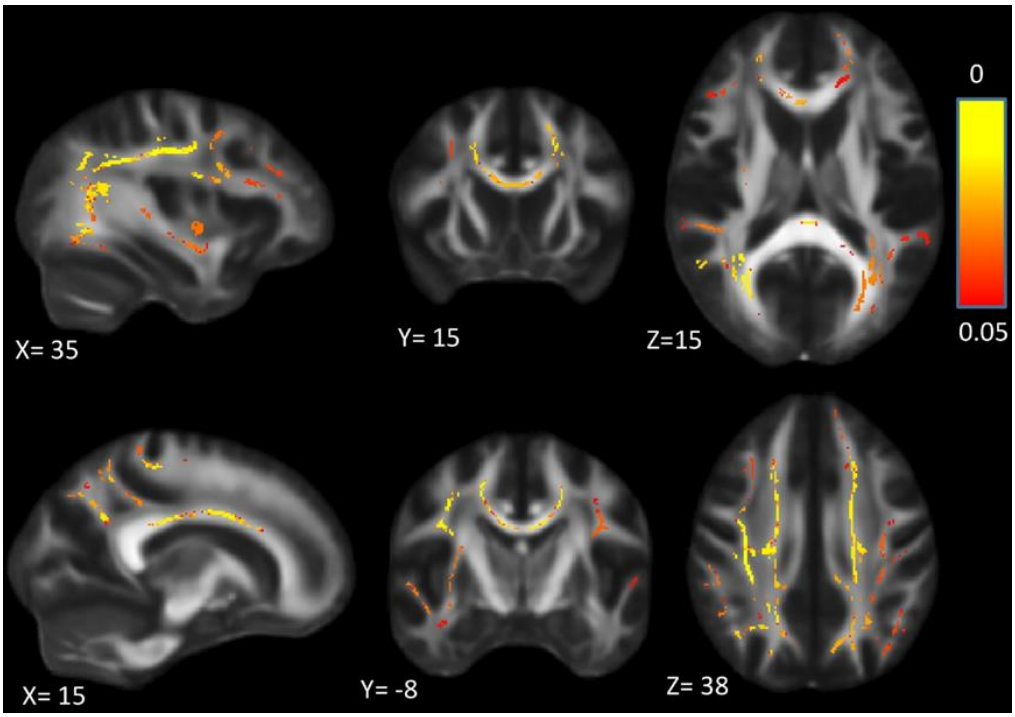

Figure 8 Mediation effects (p-values) of white-matter FA on the association between age and WM performance (high WM-load condition).

Study IV

Age-related changes in white-matter integrity and their association with decline in working memory

Xin Li, Jonas Persson.

This study is in manuscript format.

Background

Both cross-sectional (e.g., Madden et al., 2017; Peters et al., 2014; Salami et al., 2012) and longitudinal (Bender and Raz, 2015; De Groot et al., 2016; Sexton et al., 2014; Teipel et al., 2010) studies have shown that older adults have lower white-matter integrity than younger adults in most of the major white-matter tracts. Moreover, stronger negative age effects on white-matter integrity have been demonstrated in older compared to younger adults (Bender et al., 2016; Sexton et al., 2014), suggesting a non-linear age trend of change in white-matter integrity (Salami et al., 2012). Moreover, the age trends of white-matter integrity may differ between different brain regions. The anterior parts of the brain show greater decline in white-matter integrity than the posterior parts (Davis et al., 2009; Head et al., 2004; Madden et al., 2009b; Salami et al., 2012; Sexton et al., 2014).

White-matter integrity has been associated with WM (Charlton et al., 2008, 2006; I. J. Deary et al., 2006; Kennedy and Raz, 2009a; Madden et al., 2009b) and processing speed (Bucur et al., 2008; Kuznetsova et al., 2016; Lövdén et al., 2014; Madden et al., 2004a; Salami et al., 2012), but less so with episodic memory or verbal ability (e.g., Salami et al., 2012; Vernooij et al., 2009). In one longitudinal study, changes in white-matter integrity accounted for 10.8% of the variance in WM (Charlton et al., 2010). The *COMT*-Val158Met polymorphism has been associated with white-matter integrity (Papenberg et al., 2015b). Using the same sample, study III demonstrated genetic effects of *COMT* on white-matter integrity, but no effect was found for other DA-related genes, such as *DRD2/ANKK1*-Taq1A and *DRD2*-C957T. No study to date has investigated whether *COMT* influences longitudinal changes in white-matter integrity. The overall aim of this study is to explore how white-matter integrity changes with advancing age, with special focus on characterizing the patterns of the age trends across the adult life span and testing whether the changes followed an anterior – posterior gradient of greater - lesser vulnerability to aging. In addition, this study investigates how changes in white-matter integrity are associated with changes in cognition (WM and processing speed) and with *COMT*.

Methods

This study used a large sample of participants from 30 to 80 years old, who were followed 2 or 3 times (baseline, 1st follow-up, and 2nd follow-up) with 5 years between measurements. The DTI analysis was based on TBSS. First, we used PALM (Winkler et al., 2014) to conduct a 3 (time points) by 2 (age groups) repeated-measures ANOVA on FA to investigate longitudinal changes in white-matter integrity, and how age may influence these changes. Then, we extracted mean FA for seven white-matter tracts and characterized the age trajectories for these tracts using GAMMs. The age trajectories among three parts of corpus callosum (genu, body and splenium) were compared to examine whether the decline of white-matter integrity followed the anterior–posterior gradient. We then investigated whether longitudinal FA change was associated with changes in WM or processing speed. Finally, we investigated whether *COMT* influenced changes in white-matter integrity.

Results

We found that FA decreased in multiple white-matter tracts over 5-10 years in a large sample of healthy adults covering a wide age range (30-80 years old). Older adults had greater FA decline over time compared to younger adults suggesting a non-linear age trend of white-matter integrity. Comparison of age trajectories for genu, body, and splenium of corpus callosum showed faster decline in genu and body than in splenium, which suggests that changes of white-matter integrity follow an anterior–posterior gradient. In addition to the age-related decreases of FA observed in most parts of the white-matter skeleton, we observed an increase of FA with time, mainly in crossing-fiber regions, such as the cortical spinal tract, inferior fronto-occipital fasciculus, and the anterior part of superior longitudinal fasciculus. In these regions, motor-related projection fibers cross association fibers, such as the superior longitudinal fasciculus (Douaud et al., 2011). Greater white-matter integrity in these regions might reflect that the

association fibers were affected by age, whereas the cortico-spinal tract remained relatively stable over time (Douaud et al., 2011).

With regard to the associations with cognition, for WM, behavioral performance increased from baseline to follow-up in both younger and older adults, but the increase was not significant, suggesting a practice effect at least for older adults. For processing speed, performance showed significant decrease in older, but not in younger older. More importantly, we found associations between changes of FA and changes of working memory over 5 years follow-up, primarily in anterior corpus callosum (genu and body), superior longitudinal fasciculus and internal capsule, suggesting that age-related changes in WM integrity can partially account for the age-related changes in WM. No change-change association was observed for processing speed. Finally, consistent with the same analysis using the baseline data (study III), there were weak effects of *COMT* on FA at both follow-ups (lowest p = .07). No *COMT* effect was found on longitudinal FA changes.

Conclusion

Extensive decreases of white-matter FA were observed globally, except for the cortical spinal tracts, in both younger and older adults after 5-10 years follow-up. The results from GAMM, a non-parametric approach, and TBSS, supported the non-linear relation between age and white-matter integrity. In addition, the age trends were steeper in genu and body than in splenium of corpus callosum, indicating an anterior – posterior gradient of FA changes with advancing age. Moreover, using longitudinal data, our findings indicate that age-related changes in white-matter integrity might account for age-related changes in WM in older adults.

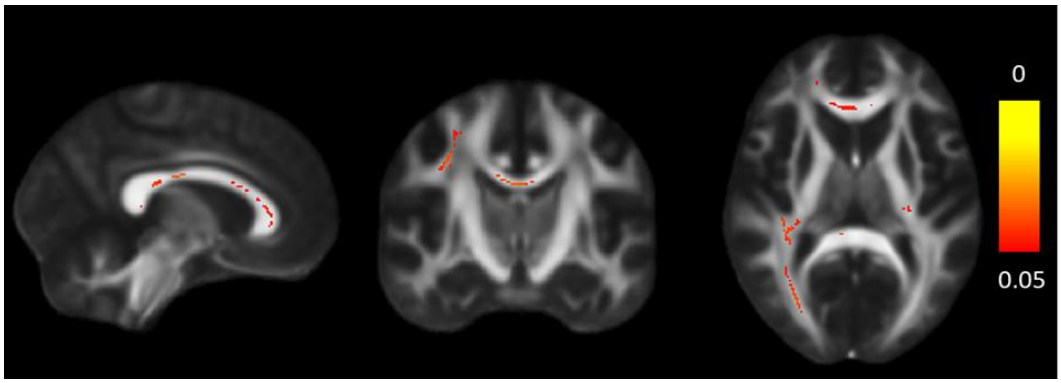

Figure 9 Associations between changes of FA and changes of WM performance from baseline to the first follow-up

DISCUSSION

The overall aim of this thesis is to investigate neural and genetic underpinnings of WM functioning in older adults, with special focus on the influence of DA-related genes on brain structural and WM-related brain functions, and its potential interaction with age. Results on the influence of aging show that (1) WM performance was lower in older than younger adults (Studies I, II and III); (2) Older adults had lower GM volume (study I and II) and white-matter integrity (Studies III) globally compared to younger adults. During WM, modulation of striatal activity was weaker in older compared to younger adults (Study II); (3) Age-related differences in white-matter integrity was linked to WM impairment in older adults (Study III). This finding was supported by longitudinal data in study IV. In study IV, both WM and white-matter integrity decline with increasing age, and changes of WM after a 5-year follow-up were associated with the changes of white-matter integrity, mainly in anterior and middle parts of corpus callosum and superior longitudinal fasciculus.

Genetic analyses were performed on three DA-related polymorphisms (*DRD2/ANKK1*-Taq1A, *DRD2*-C957T and *COMT* - Val158Met) in order to examine the relationship to WM (study II), brain structure (study I III & IV), and WM-related brain function (study II). Three main findings were obtained: (1) The A allele of the *DRD2/ANKK1* -Taq1A polymorphism, which has been associated with lower caudate DA D2 receptor availability was related to smaller caudate GM volume in older adults (>70 years) (study I); (2) There were single and additive genetic effects of two *DRD2* polymorphisms on WM performance and brain activity in PFC and caudate during a WM task, reflecting that genotypes associated with higher DA availability were beneficial to WM performance and linked to greater brain activity (study II); (3) There were weak effects of *COMT*, which has been associated with PFC DA levels, on white-matter integrity in corticospinal tracts and superior longitudinal fasciculus. In addition, analyses of age by gene interactions showed that the DA-related genetic effects on the intermediate phenotypes, such as brain structure and brain function, were observed in older, but not younger adults (study I & II), suggesting magnified genetic effects in aging. These imaging and genetics findings will be discussed below in terms of their significance and implications. Finally, methodological considerations and limitations will be addressed.

Neuroanatomical basis of age-related decline in working memory

WM functioning declines in aging; however, the extent to which brain structure can account for the age-related deterioration remains unclear. In a review of structural brain-imaging studies of cognition in older adults, Salthouse (2011) argued that there is little evidence to support the notion that brain structure measurements, such as GM volume, white-matter lesion, and white-matter integrity, are important neuroanatomical substrates of age-related cognitive decline. While some studies have found an association between GM volume and WM (e.g., Gunning-Dixon and Raz, 2003; Kennedy et al., 2009b), the results from this thesis are consistent with this notion in that no association was observed between GM volume and WM after partialing out the effect of age (study II, not reported). One possible explanation for the lack of an association between GM volume and WM might be that GM volume is a macroscopic measure,

which are the crudest of neurobiological metrics (Van Petten et al., 2004). It is also possible that some other variable that changes with increasing age, such as neuroinflammation or DA signaling, might more directly influence both GM volume and WM performance, and these two later variables might not necessarily be correlated. Another reason could be that both GM volume and WM performance are highly complex and simple associations between the two could be confounded by many other factors, such as physical activity (Papenberg et al., 2016), and cognitive training (Lövdén et al., 2013).

However, our findings from studies III and IV provide both cross-sectional and longitudinal evidence supporting that age-related differences and decline in WM performance might reflect lower/decreased white-matter integrity in older adults. The observations that WM performance was associated with white-matter integrity, but not with GM volume, are consistent with previous studies (e.g., Charlton et al., 2010), and with the notion that DTI measures of white-matter microstructure might be more sensitive to aging and cognition than volumetric measures (Giorgio et al., 2010; Hugenschmidt et al., 2008). First, we found clear associations between white matter and WM and speed after controlling for age (study III). The WM–white-matter associations were stronger in the high-demanding than in the low-demanding WM condition (study III). Highly demanding WM tasks have been associated with greater brain activity in fronto-parietal and subcortical regions, such as thalamus and caudate (Kennedy et al., 2017), and with higher fronto-striatal functional connectivity (Salami et al., 2019). Our findings extend previous work on brain activation and functional connectivity (Kennedy et al., 2017; Salami et al., 2019) to white-matter integrity, and suggest that greater integrity of structural connectivity might be needed when the task requires more multi-regional brain collaboration, such as in a high WM-load task. However, it should be noted that the load-dependent associations were observed only when using an ROI approach but not in a voxel-wise analysis. It is still unknow why the load effects were only seen in the ROI analysis. One reason could be that WM performance of both manipulation and maintenance condition were included in one model. This likely causes a collinearity problem, because the correlation between performance in the two conditions was high ($r = 0.64$). In this case, ROI analysis that based on the average FA values of one tract might be more sensitive than the voxel-wise analysis. Future studies should explore this issue using different WM tasks and statistical methods.

In addition to direct white matter – WM performance associations, we found that white-matter integrity mediated the association between age and WM (study III). This result extends previous findings that white matter mediates the age effect in executive functions (Brickman et al., 2012) and cognitive flexibility (Madden et al., 2009b). This result also provides evidence supporting the notion that white-matter microstructure might account for age-related decline in WM. In our results, both the white matter - WM associations and the white-matter mediation effects were observed across the entire white-matter skeleton, suggesting lack of regional specificity. One possible reason thereof might be that successful WM performance relies on communication and interactions between multiple brain regions (D'Esposito and Postle, 2015; Eriksson et al., 2015; Rottschy et al., 2012). Another possibility of the low degree of regional specificity could be the limitation of the TBSS methodology itself. The tract-based approach

used in studies III and IV relies on projecting the FA/MD/AD/RD values into an average skeletonized mask, which increases the accuracy of inter-individual alinement, but might lead to decreased regional specificity. It is also possible that the results demonstrating a direct white-matter – WM association or the mediation effects only include cross-sectional data, might not reflect a true causal relation between white matter and WM performance. This issue will be discussed below.

In the introduction, we proposed that white-matter microstructure in the anterior part of the brain might show greater changes than the posterior part (e.g., Madden et al., 2009b; Salami et al., 2012; Sexton et al., 2014). This notion was supported by results from study IV, which were based on both longitudinal and cross-sectional data across the adult life span. In that study, we compared age trajectories for three separate parts of corpus callosum and found that the age trends of genu and body were steeper than that of splenium after the age of 70. Using longitudinal data with a 2-year follow-up, Charlton et al. (2010) demonstrated that age-related changes in global white-matter integrity accounted for 11 % of the age-related WM decline. The observations of the anterior-posterior gradient of white matter degeneration, together with the critical role for PFC in WM functioning, make it reasonable to expect that the global change-change association found in Charlton et al's study (2010) could be largely driven by age-related decline in anterior parts of the white matter. This was supported by the findings from study IV, which demonstrated that age-related decline in white-matter integrity, especially in genu and body of corpus callosum and superior longitudinal fasciculus, was associated with age-related changes in WM. The genu and body of the corpus callosum connect the left and right hemispheres of the frontal/parietal lobes. Superior longitudinal fasciculus is an intra-hemispheric tract that connects the frontal lobes with posterior parietal and temporal lobes. The fronto-parietal network has been associated with WM performance in several studies (for a review, see Rottschy et al., 2012), and bilateral PFC engagement and frontal-parietal connectivity plays an important role in WM or executive function in older adults (Cabeza et al., 2004; Madden et al., 2010, 2007; Rieckmann et al., 2017). Thus, our findings extend previous functional imaging studies and those of Charlton et al (2010), suggesting that age-related decline in the structural connections of bilateral PFC and between PFC and posterior brain regions may be critical to impaired WM performance in aging. Although such a correlation does not imply causality, these results address the question raised by Salthouse et al. (2011), and support the view that white-matte integrity might be one of many possible neuroanatomical substrates of age-related WM impairment.

Age-related differences in working memory – related brain activity

Findings from many previous fMRI studies have indicated that one explanation for age-related decline in WM performance could be that older adults cannot up-regulate PFC activity in response to increasing task demands (Cappell et al., 2010; Kennedy et al., 2017; Mattay et al., 2006; Nagel et al., 2009; Nyberg et al., 2015, 2009). Likewise, older adults may also show reduced ability to down-regulate activation in the default-mode network when WM task demands increase (Kennedy et al., 2017; Park, 2010; Persson et al., 2007; Turner and Spreng,

2015). Our results from study II extend these observations by demonstrating that older adults have reduced modulation of striatal activity during WM compared with younger adults. Striatum is a key region engaged in WM updating and switching (Cools et al., 2004; Dahlin et al., 2008; Lewis et al., 2004; McNab and Klingberg, 2008; O'Reilly and Frank, 2006), whereas, PFC has been associated with maintaining stable representations in WM (Chee, 2004; Curtis and D'Esposito, 2003; Rypma and D'Esposito, 2000). The functional role of PFC - striatal interactions have been explored using computational modelling. This line of work has revealed that during WM, the PFC maintains goal-relevant information, and then flexibly updates WM representations when the striatum sends updating/switching signals to the PFC (Frank et al., 2001; O'Reilly, 2006; O'Reilly and Frank, 2006). Thus, age-related decrease in up-regulating the PFC (Cappell et al., 2010; Kennedy et al., 2017; Mattay et al., 2006; Nagel et al., 2009; Nyberg et al., 2015, 2009) and the striatum (study II) suggest that both WM stability and WM flexibility were impaired in older adults.

The influence of dopamine-related genes on brain structure and function in older adults

A link between brain structure and DA levels has been found in many previous studies. For example, using a voxel-wise approach, Woodward et al. (2009) reported an association between GM volume and dopamine D2 receptor availability in caudate. Chronic treatment with DA D2 receptor antagonists in adulthood has increased GM volume in basal ganglia (Chakos et al., 1994; Lieberman et al., 2005). The underlying mechanisms of this link remain unclear. One possibility is that DA have a trophic function during neuron maturation (Nieoullon, 2002). For example, activation of D2 receptors may induce neurite outgrowth (Reinoso et al., 1996), and DA-depleted rats have shown decreased length of dendrites, as well as altered neuronal density (Kalsbeek et al., 1989, 1987; Wang and Deutch, 2008).

In study I, we found smaller caudate volume in A-carriers of the *DRD2/ANKK1* – Taq1A polymorphism than in non-carriers. The A allele of this polymorphism has been associated with lower caudate DA binding (Jönsson et al., 1999; Pohjalainen et al., 1998; Thompson et al., 1997). Our results extend past research by demonstrating a link between genetically based differences in DRD2 density, and GM volume in caudate. This genetic effect was only demonstrated in older adults (> 72 years), reflecting a magnified genetic effect in aging. I will discuss more on this issue in the next section. This result also suggests that DA may influence brain structure in older adults more than in younger adults. Thus, in addition to the hypothesis of the tropic effects of DA, the DA-GM volume link observed only in older adults might be attributed to neuroinflammation in older adults. On the one hand, DA D2 receptors modulate innate immunity through αB-crystallin, which reduces neuroinflammation (Shao et al., 2013). On the other hand, higher levels of a pro-inflammatory biomarker have been associated with smaller GM volumes in middle-aged and older adults (Marsland et al., 2015; Satizabal et al., 2012). In study I, the smaller volume observed in older A carriers might be attributed to higher level of neuroinflammation, detrimental to GM integrity.

Several lines of evidence support a link between DA function and white-matter integrity (Lindholm and Jazin, 2007; Rieckmann et al., 2016; Rosin et al., 2005). White matter is mainly

made up of myelinated axons, produced by oligodendrocytes. DA agonists might directly influence oligodendrocyte differentiation, and thereby promote the formation of myelin through mature oligodendrocytes (Lindholm and Jazin, 2007). DA agonists also protect oligodendrocytes against damage from both oxidative glutamate toxicity, and oxygen–glucose deprivation (Rosin et al. 2005). The *COMT*-Val158Met polymorphism has been associated with DA levels in the PFC (e.g., Lotta et al., 1995). In addition, this polymorphism may affect white-matter integrity in several tracts, including the superior longitudinal fasciculus; forceps minor, which is a portion of corpus callosum; inferior fronto-occipital fasciculus; and cingulate gyrus (Papenberg et al., 2015b). Using a different sample with comparable size (314 in study III vs. 260 in the study by Papenberg et al., 2015b), study III and IV investigated the effect of *COMT* on white-matter integrity, and its changes after 5 years. The results showed weak *COMT* effects (lowest $p = .06$) on FA of several white-matter tracts including internal capsule, corona radiata, posterior thalamic radiation, and superior longitudinal fasciculus, but no effect was found for longitudinal changes of white-matter integrity. Together with the findings from Papenberg et al. (2015b), these results suggest a link between DA level in PFC and white-matter integrity in cortical or subcortical regions. The brain regions that demonstrated the *COMT* effects do not fully overlap between the findings from study III and IV, and Papenberg et al.'s study (2015b). One reason could be low statistical power in these studies. Future studies with larger sample sizes may be required to explore the more precisely brain regions that are influenced by *COMT*.

There is much evidence indicating that WM performance is influenced by DA levels in the brain, and age-related decreases in dopaminergic functioning might contribute to WM impairment in aging (for reviews, see Bäckman et al., 2010, 2006; Cools and D'Esposito, 2011; Li et al., 2010). WM relies on the dynamic balance between cognitive stability and flexibility, and DA functions in PFC and striatum might play separate roles in the two components of WM (for reviews, see Cools and D'Esposito, 2011). Pharmacological fMRI studies have revealed that the DA D2 receptor agonist bromocriptine can modulate striatal activity during task switching, but does not seem to affect processes related to distraction from irrelevant information in WM. In contrast, this agonist has been shown to modulate PFC activity during distraction, but not during task switching (Cools et al., 2007). Any Met carriers of the *COMT* polymorphism, who have higher DA levels in PFC, demonstrated higher PFC activity than Val/Val carriers in a highly demanding WM task (Nyberg et a., 2014). This pattern was supported by the results from study II. Here, we found that individuals carrying the genetic combination that has been associated with higher striatal DA D2 receptor density had higher caudate activity and better WM performance in an off-line 2-back task. In contrast, individuals carrying the allele associated with higher DA D2 receptor density in PFC (C carriers of the *DRD2 – C957T* polymorphism), had greater brain activity in DLPFC and better performance in the in-scanner WM task. For the in-scanner WM task (Figure 4), we observed increased brain activation in both DLPFC and caudate (Nyberg et al., 2015; Pudas et al., 2009); thus, both cognitive stability and flexibility were required during the task. However, cognitive performance in this task was only associated with brain activity in the fronto-parietal network,

but not with caudate activity (Figure 10). This observation might reflect that maintaining stable representations was critical to successful performance of this WM task. In comparison to the in-scanner WM task, performance on the offline 2-back task relies more on memory updating. Overall, the results from study II support a link between DA receptor binding and BOLD activation in the same region, and through this link, DA in PFC and caudate may play separate roles in cognitive stability and flexibility during WM. They jointly revealed that genotypes associated with higher DA function were related to greater brain activity and better WM performance.

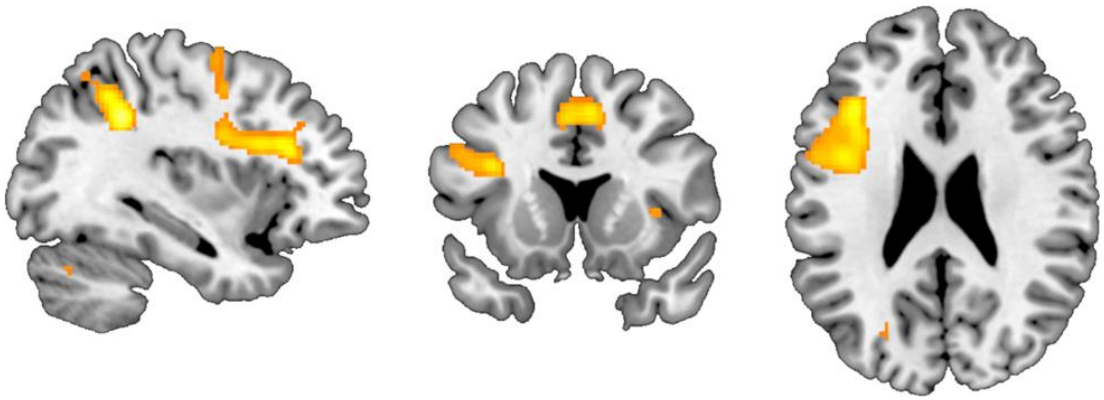

Figure 10. Brain activity in the parietal lobe, and dorsolateral and dorsomedial PFC associated with WM performance.

Age-related magnification of genetic effects

The resource-modulation hypothesis assumes that the relation between cognitive performance and brain resource across the life span is non-linear (Figure 3). Brain resource may include neurochemical and structural brain parameters, such as DA function and GM or white-matter integrity (Lindenberger et al., 2008). Since brain resources typically decline with increasing age, this assumption would be supported by evidence showing that the behavioral performance – brain resource associations are greater in older than younger adults. For example, in study III, we found that the white matter – WM associations were larger in older than younger adults, although the difference of the two slopes was not significant. Also, GM volume and cognitive performance were more strongly associated at older ages (Gunning-Dixon et al., 2009; Hedden and Gabrieli, 2004; Raz and Rodrigue, 2006; Van Petten, 2004). If the assumption is met, according to the resource-modulation hypothesis, cognitive performance would have larger variance in healthy older adults than younger adults, although the two age groups have equivalent amounts of genetic variation. Although we did not find that genetic effects on cognition was larger in older adults in our studies, this hypothesis has been supported by many previous genetic studies (for reviews, see Papenberg et al., 2015a, 2015c).

However, we observed magnified genetic effects on brain-based phenotypes for older adults. In study I and II, we found significant interactions between age and genotype, both with regard to GM volume (study I), and brain activation (study II). In both of these studies, follow-up tests showed that the genetic effects were present in older adults only. Moreover, in study III, the

genetic effects on white-matter integrity were mainly driven by the older adults, although the age by gene interaction was not significant. These results are in line with many previous studies showing larger genetic effects on brain function (e.g. Persson et al., 2015), and white-matter integrity (e.g. Papenberg et al., 2015b) in older than younger adults. As the resource-modulation hypothesis posits that available brain resources modulate the variance in behavioral performance, it can only provide explanations on differential genetic effects on behavioral-based phenotypes with age. This hypothesis does not address the question of the exact mechanisms that modulate the variance of the brain resource itself, and therefore cannot explain the enlarged genetic effects on brain-based phenotypes found in the studies mentioned above.

Gene-environment interactions and correlations could provide additional explanations for age-related magnified genetic effects on brain structure and function (Papenberg & Bäckman, 2018; Plomin and Deary, 2015; Reynolds and Finkel, 2015). For example, life style factors, such as physical activity (Erickson et al., 2013; Ferencz et al., 2014), lifetime intellectual enrichment (Vemuri et al., 2014) and healthy dietary intake (Whalley et al., 2008) can alleviate the negative effects of disadvantageous genotypes on cognitive performance. On other hand, individuals with beneficial genotypes may be more likely to choose a more stimulating or more suitable environment for developing their potentials. The environment that they have chosen will then enhance the influence of the beneficial genes they carry, and change their gene expression in a positive direction. Across the lifespan, such reciprocal gene–environment interactions may strengthen the effects of a gene and could result in stronger genetic effects in aging on either brain or cognition (Papenberg & Bäckman, 2018).

Methodological considerations

Cross-sectional vs. longitudinal designs

It is well established that longitudinal designs are more sensitive in estimating age effects than cross-sectional designs. Compared to longitudinal studies, results from the cross-sectional studies could be confounded by several factors, including sampling bias and cohort effects. In a population-based sample, the elderly samples (> 60 years) that are recruited based on voluntary participation may represent a healthier population than the general older population. For example, Nyberg et al (2010) found that the over-recruitment of PFC observed in an older sample compared to a younger sample might not reflect true age effects on PFC function, but instead be driven by a high-performing elderly subsample compared with a general young-adult sample. Moreover, age effects observed in cross-sectional studies might also be confounded by cohort-related differences in education, nutrition (e.g., Martorell, 1998) or environmental complexity (e.g., Schooler, 1998). Due to these confounders, the estimates of cross-sectional age effects are different from longitudinal age effects (Nyberg et al., 2010; Rönnlund et al., 2005).

Results from the mediation analysis in study III support the view that age-related differences in white matter account for age-related difference in WM. At first glance, the mediation analysis provides a causal relation among aging, brain, and cognition (Salthouse, 2011).

However, it has been argued that mediation models of cross-sectional data might not approximate time-dependent relations (Raz and Lindenberger, 2011). First, the associations between age and brain/cognition parameters could be nonlinear (Raz and Lindenberger, 2011). This notion was also supported by the results from study IV that white-matter changes were non-linear. Second, mediation analysis compares the estimates/coefficients of different variables (age, brain, and cognition) in a linear-regression model. However, the regression coefficients of age on brain or cognition in the model are still based on cross-sectional data, and may therefore be different from estimates of actual time-dependent age effects. Results from study IV, which found longitudinal change-change associations between white matter and WM, are therefore necessary in supporting the hypothesis that decline of white matter might contribute to WM decline in old age. It should be noted that analyses of age trajectories in study IV, and in many previous studies (e.g., Rönnlund et al., 2005; Sexton et al., 2014), should be treated with caution. This is because the life-span relations between age and the parameters of interest, such as cognition and white matter, were based on both cross-sectional and longitudinal data, and could thus be biased by the confounders discussed above.

Candidate genetic approach in genomic imaging studies

In all four studies of this thesis, we used a candidate gene approach to explore the genetic effects on brain and behavior. This approach relates brain and behavioral phenotypes to one or two functional polymorphisms, of which the molecular–genetic characteristics has been well-described. For example, the three candidate polymorphisms included in this thesis have all been associated with DA receptor densities or DA levels in PFC and striatum. However, since human cognition is modulated by complex interactions among many genes, the effect sizes of any single polymorphism are small. Thus, there are consistent failures in reproducing findings when using the candidate-gene approach. Brain function and structure can be viewed as intermediate phenotypes between gene and behavior, and it has been assumed that brain-based phenotypes have lower degree of genetic complexity, and is more 'proximal' to genetic variation than behavioral phenotypes (Green et al., 2008; Mattay et al., 2008; Meyer-Lindenberg, 2012; Rasetti and Weinberger, 2011). However, brain-based data are multidimensional, and the data analysis might introduce high "researcher degrees of freedom", which makes these imaging-genetic studies also suffer from irreproducibility. Increasing the sample sizes and the effect sizes of the functional gene of interest would help increase statistical power to detect true genetic effects, and thus reduce the probability of false-positive findings (Christley, 2010). Therefore, multiple replication studies with larger sample sizes, along with meta-analyses are required to test the effects of any candidate genes on both behavioral and brain phenotypes. Also, combining several polymorphisms would increase the effect sizes of the functional polymorphisms. For example, in study II, the joint effects of the two DRD2 polymorphisms influenced both WM performance, and its related brain functions, whereas the effect of any of the two single genes was small and undetectable. Haplotype analysis is another avenue for future studies that combine several polymorphisms in one single gene that have high statistical associations and correlate the haplotype with the phenotypes. Meyer-Lindenberg et al. (2006) related a haplotype that included 3 polymorphisms with high associations within the

COMT gene (including rs4680) to WM-related brain functions. They found the strongest effects of the *COMT* haplotype on prefrontal activation during a WM task compared with any of the single polymorphisms. Analyses based on polygenic index scores is another method that combines a number of polymorphisms in the whole genome according to their statistical contributions to phenotypic variability. Pergola et al. (2017) derived a polygenic index score that included 20 polymorphisms which were highly associated with DA D2 expression levels in PFC, and demonstrated that the polygenic index score was associated with prefrontal activity and WM reaction time. Future studies that use different methodologies for investigating gene/gene expression data would help in understanding the complex pathway from gene through brain to behavior.

Limitations

While the studies included in the current thesis have many strengths, some limitations need to be acknowledged. First, the effect sizes of Taq1A on GM volume were small. In study I, the statistical power of the genetic effects on GM volume in caudate was 0.36 with an effect size of 0.013 (eta square), and a total sample size of 387. Moreover, this effect could not be replicated in a different sample in study II. This might be attributed to the fact that the sample in study II was smaller and consisted of "younger" older adults (mean age: 73 years; n=112) compared to that in study I (mean age: 78 years; n=167). Future studies are needed to replicate the current data with larger samples of both younger and older adults.

Second, we investigated the effects of two *DRD2* polymorphisms on cognitive performance and brain functions in the PFC and the caudate. However, the DA D2 are mainly expressed in the striatum and sparsely distributed in the PFC (Camps et al. 1989; Hall et al. 1994). DA D1 receptors have the largest densities in the PFC, which is not addressed in study II. Accordingly, the effect size of the *DRD2* -C957T polymorphism on task-related PFC activity was small, and only survived an uncorrected initial $p < .005$, with a 10-voxel extent threshold. This threshold is liberal compared to the recommended $p < .001$ (Eklund et al., 2016), and may therefore increase the risk of false-positive rates. The results of these genetic effects on the PFC should therefore be treated with caution.

Third, in study III and IV, we used TBSS to analyze the white-matter data. TBSS is a relatively simple and time-saving approach to process whole-brain white-matter data. However, it has its limitation in characterizing the diffusion properties in crossing-fiber areas. For example, in study IV, we found that FA values increased with time in several tracts, such as in corticospinal tracts. This observation has been repeatedly reported in previous longitudinal TBSS studies (Bender and Raz, 2015; De Groot et al., 2016). The brain regions that showed increased FA with time, or larger FA in the patients compared to controls were located in known crossing-fiber areas (Douaud et al., 2011). Using tractography, Douaud et al. (2011) showed that the larger FA values in these regions reflected an impaired integrity in one tract combined with a preserved integrity in another tracts that intersects this tract. Other whole-brain methods on structural connectivity should be explored in future studies to investigate complex association among age, brain structure, and cognition.

Fourth, there are several factors that have been associated with both white-matter integrity, GM volume, and functional brain activation, such as BMI, hypertension and white-matter hyperintensities (Bender and Raz, 2015; Kennedy and Raz, 2009b; Madden et al., 2009a; Raz et al., 2012; Rieckmann et al., 2016; Zhang et al., 2018). In the current thesis, we did not investigate to what extent these factors influenced the relationship between brain structure/function, WM, aging, and genetic predisposition for DA availability. These factors should be considered in future studies.

Conclusions

In this thesis, we investigated the neural mechanisms of age-related changes and differences in WM, and related three DA-related genetic polymorphisms to WM performance, brain structure, and WM-related brain functions in both younger and older adults. Results showed that age-related decreases in white-matter integrity in multiple tracts might account for WM impairments in older adults (study III & IV). In addition to altered PFC function in older adults found in many previous studies (e.g. Nyberg et al., 2014), we found that older adults had lower modulation of striatal activity during WM compared to younger adults, which suggest a decrease in both stability and flexibility during WM in aging (study II). The *DRD2/ANKK1* – Taq1A polymorphism was associated with GM volume in caudate (study II). The single and additive effects of two *DRD2* polymorphisms, Taq1A and C957T, were observed on WM performance and frontostriatal brain activity during WM (study II). Variability in the *COMT* Val158Met polymorphism might influence white-matter integrity in several tracts, including cortical-spinal tract and the superior longitudinal fasciculus (study III), suggesting a link between DA activity and white-matter integrity. We also found that genetic effects on brain structure and functions were larger in older adults, which is consistent with previous genetic studies, and in line with the resource-modulation hypothesis and/or gene-environment interactions. The current studies are of importance for understanding the neural correlates of WM decline in older adults and the complex relation among DA, brain and WM. The findings provide novel insights into the functional significance of certain polymorphisms at both behavioral and neural levels.

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