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HUMAN AGING, DOPAMINE, AND COGNITION

MOLECULAR AND FUNCTIONAL IMAGING OF EXECUTIVE FUNCTIONS AND IMPLICIT LEARNING

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To my parents

ABSTRACT

Age-related deficits are legion in task switching, updating of information in working memory (WM) and inhibiting irrelevant information, collectively referred to as executive functions. Executive functions are tightly coupled to the dopaminergic system, and marked dopamine (DA) losses are observed across adulthood and aging. Several human molecular imaging studies have sought confirmation for the hypothesis that age-related DA losses are associated with deficits in executive functions in older adults. **Study I** extends this line of research by investigating the association between caudate DA D1 receptor density and functional network connectivity in younger (20-30 years) and older adults (65-75 years) using positron emission tomography and functional magnetic resonance imaging (fMRI). In line with the notion that striatal DA is a critical modulator in cortico-striato-cortical pathways, caudate D1 receptor density was significantly associated with fronto-parietal connectivity in functional brain networks related to executive functioning, and there were marked age-related reductions in DA D1 binding potential. These results show that age-related losses of caudate D1 receptors may contribute to reduced functional-network integrity in older adults.

Study II examined age differences in D1 receptor density in several striatal and cortical regions of interest. On average, D1 receptor densities were reduced by around 20 % for older compared to younger adults. Most interestingly, correlations between striatal and cortical receptor densities were reduced in older compared to younger adults, suggesting that dopaminergic losses in striatum and cortex occur relatively independently. Moreover, reduced correlations between striatal and cortical receptor densities were related to slower cognitive interference resolution in older adults. This pattern suggests that an imbalance in dopaminergic regulation between striatum and cortex may contribute to older adults' deficits in executive functions.

Implicit learning remains relatively spared in older adults despite strong associations to striatal functions and DA. This fact presents a paradox for the hypothesis that age-related DA losses mediate cognitive decline in aging. Study III and IV explore possible compensatory mechanisms, which may contribute to preserved implicit learning among older adults. **Study III** showed that increases in striatal fMRI activations during implicit sequence learning were accompanied by decreasing activation of the right medial temporal lobe (MTL) in younger adults. Older adults, however, relied on both striatum and right MTL during task performance. This pattern suggests that the MTL is not necessary for implicit learning in younger adults, but serves compensatory purposes in old age. **Study IV** used a dual-task design during fMRI acquisition in which a secondary task, designed to tax the MTL, was performed concurrent with an implicit sequence-learning task comparable to that used in Study III. Consistent with the interpretation of the data from Study III, the secondary task disrupted learning in older, but not younger adults. Moreover, differential effects of the secondary task on learning in younger and older adults were observed in activation patterns for right MTL. Collectively, the four studies provide novel insights into the mechanisms by which dopaminergic losses in aging contribute to deficits in executive functions, and suggest compensatory processes, which may account for the relative sparing of implicit learning in old age.

LIST OF PUBLICATIONS

This doctoral thesis is based on the following publications, referred to in the text by their Roman numerals.

I. **Rieckmann, A**., Karlsson, S., Fischer, H., Bäckman, L. (in press). Caudate D1 receptor density is associated with individual differences in frontoparietal connectivity during working memory. *Journal of Neuroscience.*

II. **Rieckmann, A**., Karlsson, S., Karlsson, P., Brehmer, Y., Fischer, H., Farde, L., Nyberg, L., Bäckman, L. (2011). Dopamine D1 receptor associations within and between dopaminergic pathways in younger and elderly adults: Links to cognitive performance. *Cerebral Cortex*, *21*, 2023-2032.

III. **Rieckmann, A.**, Fischer, H., Bäckman, L. (2010) Activation in striatum and medial temporal lobe during sequence learning in younger and older adults: Relations to performance. *NeuroImage*, *50*, 1303-1312.

IV. **Rieckmann, A.**, Fischer, H., Bäckman, L. Differential effects of dual-task requirements on sequence learning in early and late adulthood: Behavioral patterns and neural underpinnings. *Manuscript.*

LIST OF ADDITIONAL PUBLICATIONS

Brehmer, Y., **Rieckmann, A.**, Bellander, M., Westerberg, H., Fischer, H., Bäckman, L. (2011). Neural correlates of training-related working-memory gains in old age. *NeuroImage, 58,* 1110-1120.

Karlsson, S., **Rieckmann, A**., Karlsson, P., Farde, L., Nyberg, L., Bäckman, L. (2011). Relationships of dopamine D1 receptor binding in striatal and extrastriatal regions to cognitive functioning in healthy humans. *NeuroImage*, *57*, 346-351.

Bäckman, L., Karlsson, S., Fischer, H., Karlsson, P., Brehmer, Y., **Rieckmann, A.**, MacDonald, S., Farde, L., Nyberg, L. (2011). Dopamine D1 receptors and age differences in brain activation during working memory. *Neurobiology of Aging*, *32*, 1849-1856.

Fischer, H., Nyberg, L., Karlsson, S., Karlsson, P., Brehmer, Y., **Rieckmann, A.**, MacDonald, S., Farde, L., Bäckman, L. (2010). Simulating neurocognitive aging: Effects of a dopaminergic antagonist on brain activity during working memory. *Biological Psychiatry*, *67*, 575-580.

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LIST OF ABBREVIATIONS

DA	Dopamine
WM	Working memory
PFC	Prefrontal cortex
fMRI	Functional magnetic resonance imaging
DMN	Default-mode network
DLPFC	Dorsolateral prefrontal cortex
SRTT	Serial reaction time task
SL	Sequence learning
MTL	Medial temporal lobe
DAT	Dopamine transporter
COMT	Catechol-O-methyl transferase
MAO	Monoamine Oxidase
cAMP	Cyclic adenosine monophosphate
VTA	Ventral tegmental area
SNc	Substantia nigra pars compacta
PET	Positron emission tomography
BP	Binding potential
RT	Reaction time
AADC	Aromatic L-amino acid decarboxylase
SMS	Sensorimotor striatum
AST	Associative striatum
VST	Ventral striatum
OFC	Orbitofrontal cortex
MPFC	Medial prefrontal cortex
ACC	Anterior cingulate cortex
PC	Parietal cortex
TR	Repetition time
TE	Echo time
BOLD	Blood oxygen level-dependent response
GLM	General linear model
TAC	Time-activity curve
ROI	Region of interest
S-R	Stimulus-response
S-S	Stimulus-stimulus

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1 INTRODUCTION

1.1 COGNITIVE NEUROSCIENCE OF AGING

"Getting old" is often used interchangeably with forgetfulness, clumsiness, and general decline in physical and mental abilities. Contrary to popular belief, research over the last decades has identified that aging affects certain cognitive domains, wereas others are relatively spared (e.g., Prull et al., 2000; Salthouse, 2004). Age-related deficits are most apparent in recollection of autobiographical events (*episodic memory*) and mental operations involving cognitive control (*executive functions*). Older adults are as good as, or better than younger adults in language abilities and general knowledge (*semantic memory*), and in forms of cognition that are implicit. Implicit cognition includes the automatic acquisition of skills and procedures through practice (*implicit learning*) and facilitated processing of previously encountered stimuli (*priming*).

With the advent of functional imaging techniques, much of cognitive aging research now focuses on understanding the physiological changes that underlie cognitive performance in older adults. Understanding age-related changes in brain structure and function and how they impact cognition is vitally important for differentiating "normal" aging from age-related neuropathological changes that occur, for example, in Alzheimer's disease or Parkinson's disease. This thesis contributes to understanding the neurobiological basis of cognitive functions in healthy older adults by focusing on the association of dopamine (DA) functions with age-related deficits in executive functions and age-related changes in brain activation, and by exploring why implicit learning remains relatively spared in aging despite age-related losses in key brain structures.

1.1.1 Executive functions

Executive functions are often referred to as frontal lobe functions and the critical involvement of the frontal lobe for such functions has been confirmed in many patient and functional neuroimaging studies (e.g., Wager and Smith, 2003). Executive functions have been separated into three key components: Shifting, updating, and inhibition (Miyake et al., 2000). Shifting concerns flexible switching between tasks or rules. Updating is akin to the concept of working memory (WM) as originally proposed by Baddeley & Hitch (1974). WM involves the temporary maintenance and manipulation of information over several seconds. Lastly, inhibition relates to the suppression of pre-potent responses. Most cognitive tasks tapping executive functioning can be associated more strongly with one component of executive functions over another. One of the most widely used tasks of executive functioning, the Wisconsin Card Sorting Task is most strongly linked to set shifting (Miyake et al., 2000). Tests of WM such as N-back tasks primarily assess updating, and tasks that require interference resolution like the Stroop task or Go/NoGo tasks assess inhibitory control.

Age-related deficits in executive functioning are well documented and generalize across set shifting tasks, WM tasks and inhibitory control tasks (Salthouse et al., 1996; 2003; Gunning-Dixon and Raz, 2004; Reuter-Lorenz and Sylvester, 2005). For WM tasks in particular, age deficits increase with increasing task load and deficits are more pronounced in tasks that require complex manipulation, rather than simple maintenance, of the material (Dobbs and Rule, 1989; Salthouse and Babcock, 1991). Over the last 20 years, functional magnetic resonance imaging (fMRI) has become

widely available as a technique for studying neural activation during cognitive task performance. However, the patterns of neural activation underlying executive dysfunction in aging are not straightforward (see Buckner, 2004; Reuter-Lorenz and Sylvester, 2005; Grady, 2009; for reviews). Decreased recruitment of the prefrontal cortex (PFC) and other task-relevant areas has been observed in older adults during executive tasks, which has been interpreted in terms of reduced neural functioning in aging (e.g., Jonides et al., 2000; Mattay et al., 2006; Zarahn et al., 2007; Holtzer et al., 2009). At the same time, increased bilaterality in PFC activation among older adults has been shown in several studies of executive functioning (e.g., Nielson et al., 2002; Cabeza et al., 2004; Grady et al., 2008; Madden et al., 2007; Zhu et al., 2010). The fact that some of the latter studies have found positive associations between greater frontal bilaterality and performance in older adults supports the hypothesis that reduced asymmetry in aging reflects compensatory processes (Cabeza, 2002). However, it remains to be determined how findings of decreased and increased frontal recruitment in aging can be successfully integrated.

More recently, fMRI studies of executive functioning in older adults have started to focus on age-related changes in functional network connectivity. Functional connectivity analysis is a type of fMRI analysis, which assesses how well the time series of one brain area or voxel correlates with that of another brain area or voxel. In contrast to those fMRI analyses which focus on identifying areas in the brain that collectively respond to stimuli on- and offset, connectivity analyses identify functionally related brain networks, often independent of task condition. Two brain networks have emerged that are important for executive functions: the fronto-parietal "executive control" network and the default-mode network (DMN). The fronto-parietal network (Figure 1) encompasses the dorsolateral PFC (DLPFC), premotor cortex, the parietal cortices surrounding the intraparietal sulcus and the striatum and is engaged during executive tasks (Seeley et al., 2007; Toro et al., 2008). The DMN involves the ventro-medial prefrontal cortex, the posterior cingulate, the inferior parietal lobule and temporal areas including the hippocampus and is engaged during self-reflective thought and "mind-wandering" (Greicius et al., 2003; Buckner et al., 2008). Activation of the fronto-parietal network and deactivation of the DMN has been linked to better task performance (Kelly et al., 2008; Hampson et al., 2010) and increase with greater task difficulty (McKiernan et al., 2003; Nagel et al., 2011) in younger adults. Several studies have shown that connectivity in the fronto-parietal network and the DMN decreases with age and is related to deficits in executive functioning (e.g., Andrews-Hanna et al., 2007; Sambataro et al., 2010). Paralleling the findings of task-based analyses, increased bilateral prefrontal connectivity in older adults has been found in one study (Grady et al., 2010).

1.1.2 Implicit learning

Implicit cognitive functions describe learning and memory beyond an individual's awareness. Implicit learning refers to the acquisition of cognitive and motor skills through repeated performance without awareness. Implicit learning is at the core of our everyday behavior. Cycling to work, opening the door, speaking in a grammatically correct way are all example of skills that we "just do" without being able to verbalize how, or being able to pinpoint learning to a specific point in time. In the experimental setting, implicit learning is tested with tasks that conceal the real nature of the task. Performance is expressed as improvement of task performance in the absence of awareness of the to-be-learned material. The Serial Reaction Time task (SRTT) is frequently used to assess implicit learning of a motor sequence.

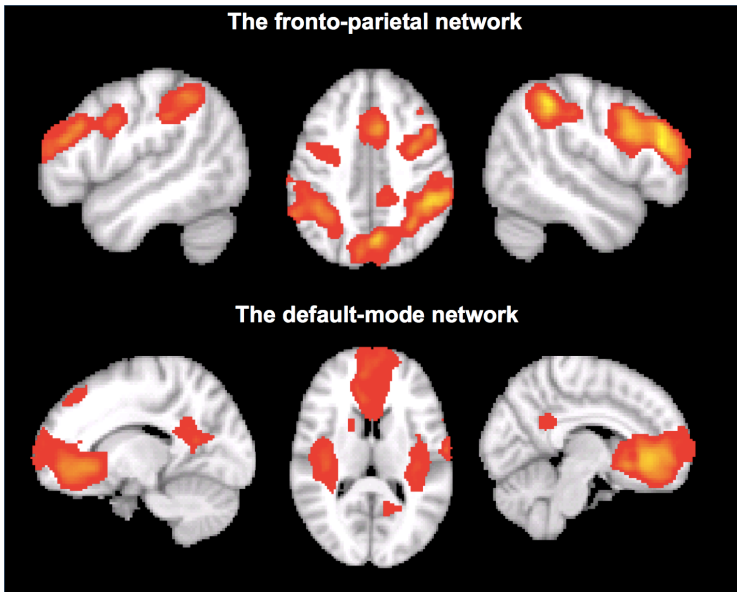

Figure 1. The fronto-parietal network and the default-mode network. Based on a functional connectivity analysis in younger adults from Study I. Seeds are the dorsolateral prefrontal cortex for the fronto-parietal network and the medial prefrontal cortex for the default-mode network

Here, the participant is required to make seemingly random button presses but, unbeknownst to the participant, trials follow a sequence or rule. Decreasing reaction times in the absence of sequence awareness is taken as evidence for implicit motor sequence learning (SL). Implicit learning of motor sequences and rules depends on the striatum. This has been shown both in fMRI studies in healthy younger adults (Grafton et al., 1995; Rauch et al., 1997; Peigneux et al., 2000; Reiss et al., 2005) and in individuals with striatal dysfunction like in Parkinson's and Huntington's disease who show select deficits in implicit learning (Knowlton and Squire, 1996; Siegert et al., 2006, for review). Implicit motor sequence learning has also been linked to activation of the prefrontal and premotor areas, parietal areas and the cerebellum (Poldrack et al., 2005).

Implicit learning received considerable theoretical attention in the 1980s and 90s (e.g., Reber et al., 1989; Reed and Johnson, 1994; Seger, 1994; Shanks and St. John, 1994). However, little attention has been paid to implicit learning in aging, both in comparison to implicit learning research in younger adults and patients, and in comparison to the wealth of literature on aging and explicit forms of cognition. Behavioral studies on implicit learning in aging generally show small, if any, age-related performance differences (see Rieckmann and Bäckman, 2009, for review). This may explain the lack of interest in the neural basis of implicit learning in aging. To date, few studies have investigated neural activation during implicit learning in old age (Daselaar et al., 2003; Aizenstein et al., 2005; Fera et al., 2005). These investigations show inconsistent patterns across studies with findings of greater posterior cortical recruitment in older adults (Fera et al., 2005), greater anterior cortical recruitment in older adults (Aizenstein et al., 2005) and no age differences in activation (Daselaar et al., 2003). A closer look at studies on patients with Parkinson's disease and Huntington's disease opens up a more hypothesis-driven avenue for research on the neural basis of implicit learning in aging. Despite strong associations between implicit learning and striatal functions, there are some studies in patients with early Parkinson's disease or Huntington's disease that found implicit learning to be unaffected (Dagher et al., 2001; Moody et al., 2004; Voermans et al., 2004; Beauchamp et al., 2008). These studies

have suggested that implicit learning in patients was spared because they recruited other brain regions, specifically the medial temporal lobe (MTL), which was interpreted as compensatory neural reorganization. A recent study followed 13 individuals with Parkinson's disease over two years (Carbon et al., 2010). They found that patients who maintained performance in a motor sequence learning task over two years showed increased MTL activation from time 1 to time 2, compared to patients who exhibited performance decline over time.

1.2 THE DOPAMINE SYSTEM

DA was discovered to be a catecholamine neurotransmitter in the 1950s by Arvid Carlsson, who received a Nobel Prize for his work on DA in 2000. It is now well established that DA plays a crucial role in the regulation of motor functions, learning and memory, and reward-seeking behavior. Neurodegenerative disorders such as Parkinson's disease and Huntington's disease, neuropsychiatric disorders like schizophrenia, Tourette's syndrom, and attention deficit hyperactivity disorder, as well as drug abuse and other forms of addiction are all associated with dysfunction of the dopaminergic system (see Agid and Hartmann, 2010; Abi-Dargham et al., 2010; Koob and Moal, 2010, for reviews).

1.2.1 Receptors

At the synaptic level, nerve impulses trigger the release of DA into the synaptic cleft where it binds to postsynaptic DA receptors and is cleared from the synapse via the DA transporter (DAT). The prefrontal cortex is devoid of DAT. Here, the norepinephrine transporter clears DA, and the enzymes catechol-O-methyl transferase (COMT) and monoaminoxidase (MAO) also play an important role in the degradation of DA. Postsynaptic DA receptors are commonly grouped into D1-like receptors (D1 and D5, from hereon referred to as D1) and D2-like receptors (D2, D3, and D4; from hereon referred to as D2). In the striatum, the area richest in dopaminergic innervation, D1 and D2 receptor expression separates into the direct D1-modulated and indirect D2-modulated pathway (Figure 2A). When DA is released as burst (or *phasic*) firing in response to salient stimuli, it preferentially stimulates D2 receptors, whereas transient baseline (or *tonic*) firing of dopaminergic neurons stimulates D1 receptors. At the postsynaptic membrane, stimulation of D1 receptors leads to activation of cyclic adenosine monophasphate (cAMP), whereas D2 receptor stimulation inhibits cAMP (Stoof and Kebabian, 1981). cAMP is, in turn, critically involved in postsynaptic signal transduction. Taken together, D1 and D2 receptors in the striatum exert opposite but complementary functions. Disturbance of the D1-D2 pathway balance is the hallmark of movement disorders. For example, akinesia in Parkinson's disease is thought to be the result of relative increased activity in the indirect pathway and decreased activity in the direct pathway (Gerfen, 2010). Compared to striatum, the majority of DA receptors in cortex are of the D1 subtype (Seamans and Yang, 2004).

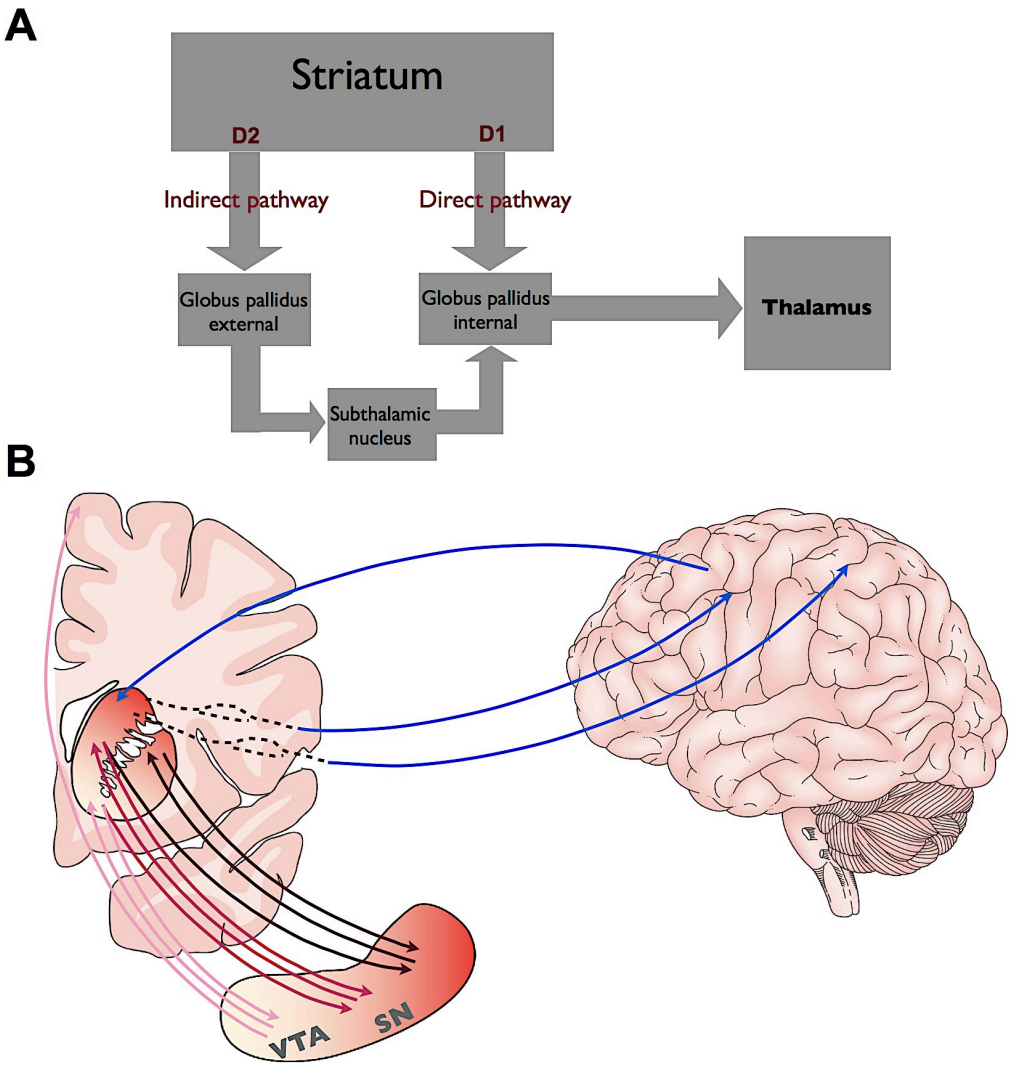

Figure 2. Major pathways. A) Schematic illustration of the direct and indirect striato-thalamic pathways. B) Schematic illustration of dopaminergic connections between midbrain, striatum, and cortex in red (Haber and Knutson, 2009). Cortico-striato-thalamo-cortical loops with a closed frontal loop and an open fronto-parietal loop (Joel and Weiner, 1994) in blue. Dotted line reflects striato-cortical connections via the direct and indirect pathways, modulated by D1 and D2 receptors respectively, and illustrated in detail under 2A. VTA – Ventral tegmental area, SN – Substantia nigra

1.2.2 Major Pathways

DA is an important neuromodulator in neocortex and striatum. Its modulatory role is probably best described in the striatum, where dopaminergic modulation is critical to the regulation of glutamatergic input from cortex to striatum and output from thalamus back to cortex. These cortico-striato-thalamo-cortical projections were originally described by Alexander et al. (1986) as parallel loops, which are functionally and anatomically segregated. Accordingly, the striatum receives input from limbic, associative and motor cortical areas, which is relayed to the area of origin via the basal ganglia and thalamus through the direct pathway or indirect pathway (Figure 2A). It was suggested later that this circuitry is not closed, but also involves open pathways where cortical input and output areas are anatomically distinct (Joel and Weiner, 1994; Figure 2B).

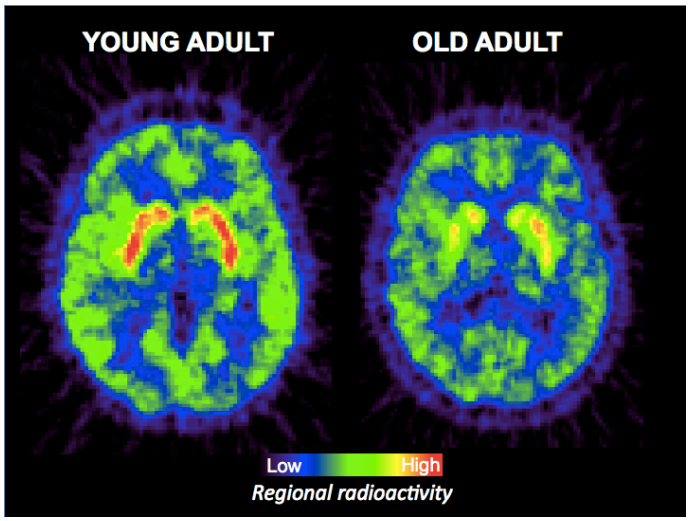

Figure 3. Example of a PET image depicting regional radioactivity after injection of the DA D1 ligand [^{11}C] SCH23390 for one young and one old adult. Images are derived from two participants of Study I and II

DA is synthesized in the ventral tegmental area (VTA), and substantia nigra pars compacta (SNc) of the midbrain. Dopaminergic projections from the SNc to the dorsal striatum via the nigrostriatal pathway constitute the majority of midbrain projections. The dorsal striatum comprises caudate and putamen, which are also referred to as associative and sensorimotor striatum, because of their respective connections with associative and motor cortical areas. The VTA, located medial to the SNc, has dopaminergic connections to the ventral striatum (nucleus accumbens; also sometimes referred to as limbic striatum because of its connections to the limbic system) and prefrontal cortices via the mesolimbic and mesocortical pathways (Figure 2B). There are also pathways from striatum to both VTA and SNc, and these are organized such that the dorsal striatum projects to SNc, and ventral striatum to VTA. However, ventral striatum projections also extend laterally to the SNc. In this way, the midbrain-striatal projections and the striatal-midbrain projections form a "spiral"-like pathway. This pathway allows for indirect connections between the ventral and dorsal striatum, which in turn receive input from different cortical areas (Haber et al., 2000; Figure 2B). In addition to the open cortico-striato-thalamo-cortical pathways described above, midbrain-striato-midbrain spiral circuits therefore allow for information transfer between limbic, associative, and motor cortical areas (Joel and Weiner, 2000).

1.2.3 Imaging Dopamine

DA receptors and other markers of the DA system can be visualized and quantified with positron emission tomography (PET). PET allows in vivo imaging of molecules in humans. Radioactively labeled ligands are injected into a person's blood stream and selectively bind to the component of interest. As the ligand decays, a positron is emitted. When the positron coincides with an electron shortly after, annihilation results in emission of a pair of γ rays. γ rays are detected by the PET system and used to infer ligand concentration at various time points throughout the PET scan. Images are then reconstructed to show radioactivity at each time point or as an image summated across time (Figure 3). Reference tissue models can be used to estimate concentration of the compound of interest based on dynamic radioactivity data. Reference tissue models are mathematical models that are fitted to the time-activity curves (TAC, radioactivity plotted against time, corrected for decay) for the region of interest (e.g., striatum) and for a reference region, which is known to be devoid of the receptor (e.g., cerebellum).

Process	Target	Example of commonly used ligands
DA synthesis	AADC	[^{18}F]FDOPA; [^{18}F]FMT
Transport to synaptic vesicle	VMAT2	[^{11}C]-DTBZ
Degradation	MAO	[^{11}C]-clorgyline; [^{11}C]-deprenyl
Reuptake	DAT	[^{11}C]cocaine; 125I-β-CIT; [^{11}C]methylphenidate
Receptor binding	D1	[^{11}C]SCH23390; [^{11}C]NNC112
	D2	[^{11}C]raclopride; [^{18}F]fallypride; [^{11}C]FLB457

Note. AADC = aromatic L-amino acid decarboxylase; VMAT2 = vesicular monoamine transporter; MAO = monoamine oxidase; DAT = dopamine transporter

Table 1. Ligands for PET imaging of the DA system

The primary parameter of interest is the binding potential (BP), an estimate of specific-to-nonspecific binding, which is used in Study I and II to infer receptor density in the regions of interest.

Molecular imaging of the DA system in humans first started in the 1980s, following the initial work of Wagner et al. (1983), when studies succeeded in selectively visualizing DA receptors with [^{11}C]raclopride and [^{11}C]SCH23390 (Farde et al., 1986, Sedvall et al., 1986). Since the 1980s hundreds of radioligands have been developed for PET imaging of the DA system (Cumming, 2009). Table 1 summarizes some of the more frequently used ligands in relation to different aspects of the DA system. Studies I and II are based on data collection in healthy younger and older adults using [^{11}C]SCH23390, the most widely used ligand for imaging of D1 receptors. [^{11}C]SCH23390 has been shown to yield reliable measurements of D1 receptor binding in striatum and cortex (Chan et al., 1998; Hirvonen et al., 2001). However, more recently, the selectivity of [^{11}C]SCH23390 in cortex has been questioned and it has been suggested that up to 25 % of the cortical signal may be due to binding to serotonin 2A receptors (Ekelund et al., 2007), a concern that is shared by many ligands used for cortical imaging of the DA system (e.g., [^{11}C]NNC 112, cocaine, [^{3}H]spiperone).

1.2.4 The Role of Dopamine in Cognition

The dopaminergic system has long been thought of as regulating primarily motor functions. More recently, patient studies (Brooks and Pavese, 2010), pharmacological manipulations of the DA system in healthy participants (Kimberg et al., 1997; Mehta et al., 2000), insights from computational modeling (Cohen and Frank, 2009), and molecular imaging studies of the DA system have established a firm link between DA and cognition. Relevant molecular imaging studies in humans are briefly reviewed below.

One approach to studying the relationship between DA and cognition using molecular imaging is to assess availability of DA markers using PET (or single photon emission tomography) while the participant rests, and link BP to performance on cognitive tests or fMRI activation assessed before or after the scan. In healthy younger adults, this method has yielded positive correlations between striatal DA synthesis capacity and

WM (Cools et al., 2008), striatal D1 receptor density and interference resolution (Karlsson et al., 2009), striatal D2 receptor density and PFC activation during updating of long-term memories (Nyberg et al., 2009), and between DA synthesis capacity and task-induced deactivation of areas associated with the DMN (Braskie et al., 2011). Studies have also shown negative associations of caudate DA synthesis capacity to executive functioning (Braskie et al., 2008) and delayed recognition (Braskie et al., 2011) and of striatal D2 receptor density to SL (Karabanov et al., 2010) suggesting that the relationship between striatal DA and cognition is not always straightforward. Although of potential interest, two of the latter observations stem from the same participants (Braskie et al., 2008; 2011) and should be interpreted cautiously in the absence of replication.

The original description of cortico-striato-thalamo-cortical circuits in which striatal DA plays a crucial role has posited parallel circuits that are functionally independent. It is now known that cortico-striato-thalamo-cortical circuits are not completely independent and integration of information processing across circuits is likely needed for efficient cognitive performance (Haber et al., 2011, for review). Nevertheless, PET studies in humans have found some evidence for functional segregation of striatal sub-compartments. Accordingly, receptor densities in ventral striatum (nucleus accumbens) appear more tightly linked to episodic memory compared to the associative striatum or sensorimotor subdivisions of the striatum (Cervenka et al., 2008) whereas the sensorimotor striatum may be linked more closely to processing speed and motor functions (Karlsson et al., 2011; Reeves et al., 2005). The associative striatum with its widespread connections to the prefrontal cortices shows the most general correlations with cognition as demonstrated by associations including general knowledge (Karlsson et al., 2011), WM (Cools et al., 2008), and verbal fluency (Cervenka et al., 2011).

An alternative approach to studying the relationship between DA and cognition is to observe displacement of a PET ligand during cognitive task performance rather than computing *post-hoc* correlations between resting state PET and cognitive task performance. Although advantageous because of simultaneous assessment of performance and DA functions, this method is currently hindered by the availability of ligands that are suitable for displacement scans. The assumption of displacement is that endogenous DA released during performance of a cognitive task competes with the ligand for binding to the receptor. Accordingly, a decrease in BP of the ligand during task performance, compared to a control condition, is assumed to reflect DA release during cognitive task performance. However, to date only [^{11}C]raclopride has been fully validated to be vulnerable to endogenous DA release. For assessment of extrastriatal DA release, [^{11}C]FLB457 and [^{18}F]fallypride have been used (Slifstein et al., 2004; Vandehey et al., 2010), but the sensitivity of FLB457 to displacement is debated (Aalto et al., 2009; Vandehey et al., 2010). The first Raclopride displacement study in healthy adults was conducted by Koepp et al. (1998), who showed evidence for striatal DA release during video-game playing compared to a resting state PET scan. Moreover, this study found strong correlations between percent reduction in BP with video-game playing and performance on the video game, indicating a positive relation between DA release and goal-directed motor functions and response selection. Evidence for DA release during cognitive task performance has since been observed during mental arithmetic (Montgomery et al., 2006) and tests of executive function (Aalto et al., 2005; Monchi et al., 2006; Lappin et al., 2008; Sawamoto et al., 2008) as well as during processing of aversive compared to neutral stimuli (Badgaiyan et al., 2010). Noteworthy, in contrast to negative correlations between DA and SL in resting state PET (Karabanov et al., 2010), displacement studies have shown DA release

during implicit and explicit SL (Badgaiyan et al., 2007, 2008; Garraux et al., 2007), which is consistent with evidence from patient (Carbon et al., 2004) and animal (see Packard and Knowlton, 2002, for review) studies that have suggested a central role for striatal DA in SL.

The bulk of human imaging work has focused on striatal DA and cognition. This may reflect the fact that ligands for the D2 receptor and DAT are more readily available than ligands that are suitable for cortex. In contrast to human studies, animal research has extensively focused on the role of DA in the PFC. Central to this body of work was an early study by Brozoski et al. (1979), which showed that local administration of a DA receptor antagonist in monkey PFC induced WM deficits. Subsequent research in primates and rodents confirmed a selective role for prefrontal D1, but not D2, receptors in WM (Sawaguchi and Goldman-Rakic, 1991) and suggested that the relation between prefrontal DA and WM follows an inverted U shape (e.g., Zahrt et al., 1997): Either too little or too much DA is detrimental to cognitive performance. The inverted U shape of DA-related functioning has been demonstrated in humans using pharmacological manipulation and behavioral genetics (see Cools and D'Esposito, 2011, for review), but human molecular imaging studies on the role of DA in PFC are rare. Takahashi et al. (2008) acquired PET data with both [^{11}C]SCH23390 and [^{11}C]FLB457 and found evidence for an inverted U shape between PFC D1, but not D2, receptor density and performance on the Wisconsin Card Sorting Test. This finding is consistent with animal research that has proposed a selective role for prefrontal D1 receptor in cognition. However, this finding was not replicated in another study (Karlsson et al., 2011) and MacDonald et al. (2009) found linear relationships between prefrontal D2 receptors and response consistency, suggesting that the relationship between prefrontal DA and cognition in humans may not be limited to D1 receptors.

Evidence from research in animals and humans clearly converges to suggest an important role for striatal and prefrontal DA in executive functions, especially in WM. The precise mechanisms by which DA contributes to cognitive functioning remain unknown. On a general level, it has been suggested that striatal DA plays a role in gating and updating of existing prefrontal representations (e.g., Frank and O'Reilly, 2006), whereas prefrontal DA may be related to stabilizing prefrontal representations and enhancing signal-to-noise ratios (e.g., Durstewitz et al., 2000). On this view, DA plays a crucial role in stability as well as flexibility (Cools and D'Esposito, 2011), which may explain its complex relation to human executive functioning.

1.2.5 Age-related Changes in the Dopamine System

There is pervasive evidence from human cross-sectional studies that DA functions decrease throughout the adult lifespan and this body of literature has been reviewed extensively (e.g., Reeves et al., 2002, Bäckman and Farde, 2004; Bäckman et al., 2006; 2010). Various markers of the DA system indicate declines of around 5 to 10 % per decade throughout adulthood for striatal D1 receptors (e.g., Wang et al., 1998), striatal D2 receptors (e.g., Antonini et al., 1993), and DAT (e.g., van Dyck et al., 1995). Studies on age-related changes in cortical DA functions also suggest declines of around 5 to 10 % per decade for D1 and D2 receptors in PFC and medial-temporal areas (Suhara et al., 1991; Kaasinen et al., 2001).

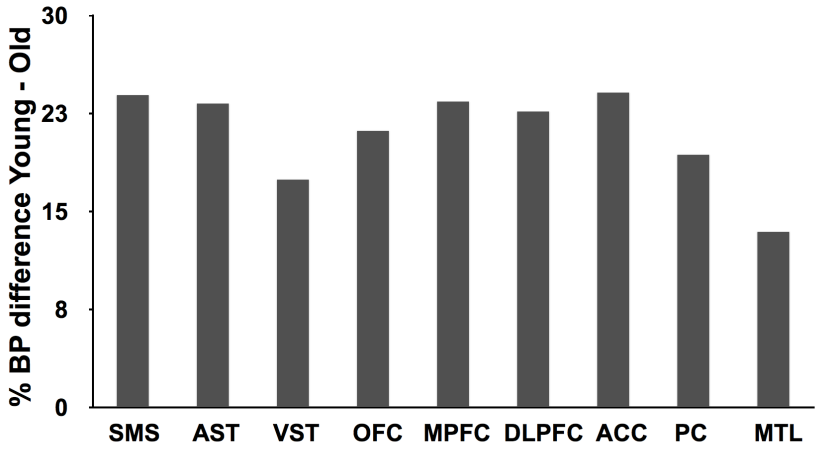

Figure 4. Percent difference in BP of [^{11}C]SCH23390 between younger (20-30) and older (65-75) adults. Regions of interest are sensorimotor striatum (SMS), associative striatum (AST), ventral striatum (VST), orbitofrontal cortex (OFC), medial prefrontal cortex (MPFC), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), parietal cortex (PC), and medial temporal lobe (MTL). Adapted from Study II.

Figure 4 (from Study II) portrays mean D1 receptor losses in striatum, cortex, and the limbic system for a sample of healthy older adults between 65-75 years of age in comparison to younger adults between 20 and 30 years of age.

The biological mechanisms that underlie DA losses in aging are not fully understood, but multiple causative factors are probably involved. These include neuronal loss (Fearnly and Lees, 1991) that may partly stem from oxidative stress (e.g., Loo and Roth, 2000; Yoo et al., 2003), loss of synapses (Colman et al., 1997; Mora et al., 2007), as well as losses of specific proteins per neuron (Mesco et al., 1993). Thus, the down-regulation of DA systems in aging may occur at multiple levels in the central nervous system.

1.3 THE CORRELATIVE TRIAD: AGING, DOPAMINE & COGNITION

It is clear that (1) healthy aging is associated with decline in executive functions and changes in brain activity during cognitive task performance, (2) DA is linked to executive functions in healthy young adults, (3) pre- and postsynaptic markers of the human DA system show strong age-related losses throughout the adult lifespan. These observations have led to the idea of the "correlative triad" among aging, DA, and cognition and the hypothesis that decline in DA functions with increasing age mediates age-related deficits in many cognitive functions (Bäckman et al., 2006). A series of studies has addressed this hypothesis. The first PET study that examined relations of DA to cognition in an age-heterogenous sample (range 24 – 86 years) was conducted by Volkow et al. (1998). They found that individual differences in [^{11}C]raclopride binding to striatal D2 receptors were associated with individual differences in motor functions and tests of executive functions, even after accounting for the effects of chronological age. Bäckman et al. (2000) extended these findings to show an age-independent association between striatal D2 binding and tests of perceptual speed and episodic memory, indicating a relatively global relationship between striatal D2 receptors and cognitive changes in old age. Reeves et al. (2005) also reported a positive association between caudate D2 receptor density and visuo-spatial WM and between

putamen D2 receptor density and motor functions in a sample of 55-90 year olds, which remained significant after controlling for chronological age. Two studies also demonstrated significant associations between striatal DAT binding and cognition in age-heterogenous samples and showed that DAT concentration could account for age-related decline in episodic memory and executive functions (Mozely et al., 2001; Erixon-Lindroth et al., 2005).

Subsequent research investigated the mediating effects of DA on age-related changes in brain activity as assessed with fMRI. Landau et al. (2009) found a positive correlation of DA synthesis capacity to WM performance and related PFC activation in a sample of 55-85 year old healthy adults, and associations between DA synthesis capacity and frontostriatal connectivity (Klostermann et al., 2011). These findings were corroborated in an age-comparative study including younger (20 – 30 years) and older adults (65 – 75 years) showing that age-related under-recruitment of the frontal and parietal cortices during WM was associated with DA D1 receptor densities in striatum and frontal cortex, even after accounting for chronological age (Bäckman et al., 2011). Two studies (Fischer et al., 2010; Morcom et al., 2009) have aimed to go beyond the demonstration of mere associations by using pharmacological DA manipulations in younger adults in an attempt to "simulate" cognitive and brain aging. Fischer et al. (2010) showed that administration of a D1 receptor antagonist led to reduced WM performance and a reduced WM load effect in frontal and parietal regions in younger adults. Another study also reported activation changes in younger adults under the influence of a D2 antagonist in inferior frontal gyrus during encoding of words for subsequent recall (Morcom et al., 2009). However, in the same study, administration of a D2 agonist to older adults did not make older adults resemble younger adults' pattern of performance and brain activity.

1.4 SUMMARY AND STUDY OBJECTIVES

Taken together, evidence gathered so far suggests that individual differences in pre- and postsynaptic DA markers are associated with individual differences in cognitive performance, over and above their common associations with chronological age.

As described above, striatal DA is a crucial modulator in cortico-striato-cortical pathways. Yet, studies that have combined molecular DA imaging and fMRI have focused on relations of DA and age to regional task-related activations or deactivations, rather than on cortical network connectivity. To date, only one previous study has investigated the relationship between striatal DA and connectivity of the PFC and striatum (Klostermann et al., 2011), but this study did not investigate connectivity between cortical areas. **Study I** in this thesis addresses the association of striatal DA D1 receptors and age-related changes in functional connectivity in two cortical networks that are implicated in executive functions, the fronto-parietal network and the DMN.

Most research has focused on striatal DA and relations to age, cognition, and associated brain activity. This bias in the literature probably reflects the scarcity of ligands that are suitable for assessment of both striatal and cortical DA functions. Molecular imaging studies in this thesis use a D1 receptor ligand [^{11}C]SCH23390 that has high affinity to both striatal and extrastriatal D1 receptors. **Study II** is therefore in the rare position to assess age-related changes in both striatum and cortex and to (1) investigate whether the magnitude of age-related losses of D1 receptor densities are comparable in striatum

and cortex, and (2) whether they occur hand in hand (i.e., are correlated), despite the fact that different DA pathways innervate striatum and cortex. Moreover, as outlined above, both striatal and cortical DA have been linked to executive functions and Study II also examines how the relationship between D1 receptor densities in striatum and cortex in aging may affect executive functions.

Whereas Studies I and II were designed to examine the hypothesis that DA plays a crucial role in age-related impairment of executive functions and associated brain network connectivity, **Studies III and IV** explore why "the correlative triad" may not hold in the case of implicit learning. As reviewed above, past research has shown that implicit SL is relatively spared in aging despite the fact that SL heavily involves the striatum and the dopaminergic system. Studies III and IV use fMRI during SL in younger and older adults to identify possible compensatory mechanisms that may explain why SL is well preserved in aging.

2 AIMS

This thesis aims to contribute to our understanding of the role of DA in age-related changes in cognitive functions. The specific research questions addressed are:

(1) **Study I**: Can age-related change in striatal DA D1 receptor density account for changes in cortical functional connectivity in aging?

(2) **Study II**: Are striatal and cortical DA D1 receptor densities correlated in adulthood and aging, and what are the implications of potential age-related changes in striatal-cortical correlations for executive functions?

(3) **Study III & IV**: Can compensatory mechanisms explain the relative sparing of implicit sequence learning in aging?

3 METHODS

3.1 PARTICIPANTS

Participants in all four studies were healthy younger (20-30 years) and older (65-75 years) adults from the Stockholm area. All participants were right-handed, Swedish speaking volunteers that were recruited by newspaper adverts. Exclusion criteria were history of past or present psychiatric or neurological disease, use of blood-thinning medication and contra-indications to MRI. In addition, for Studies III and IV a neurologist evaluated T1 and T2 weighted MRI scans for abnormal levels of atrophy and lesions.

Table 2 presents demographic information and cognitive performance on standard neuropsychological tests. The table shows that participants perform as expected for their respective age group, with younger adults outperforming older adults on tests of processing speed, episodic memory, and executive functions, and older adults performing as well as younger adults, or even better, on tests of vocabulary and verbal fluency.

3.2 COGNITIVE ASSESSMENT DURING BRAIN IMAGING

For Studies I, III, and IV, cognitive tasks were presented during fMRI acquisition. In Study II a cognitive task was performed during PET scanning. All tasks were computerized using Eprime (Psychology Software Tools Inc.) and responses were collected using custom-made response pads.

Study I: In Study I, a spatial WM task was used. Participants saw a 4 x 4 grid. Four (low load) or six (high load) positions on the grid lit up consecutively for 900 msec and, after a delay of 2 sec, a probe appeared. Performance data were analyzed using an Age (young/old) x Load (low/high) ANOVA, with reaction time (RT) and accuracy data as the dependent variables.

Study II: During the PET scan, for which data is reported in Study II, participants performed the Multi Source Interference Task (Bush et al., 2003), which taxes interference resolution. Participants were presented with combinations of three digits and asked to indicate the digit that was different by pressing one of three buttons. For control trials, the target was always congruent with the position (e.g., the digit 1 was in the first position), in a larger font size than the 2 distracters, and the distracters were always 0s (e.g., 100). For interference trials, the target was different from the corresponding position, and distracters were other digits that could be either larger or smaller than the target (e.g., 211 or 232). RT differences between control and interference trials were used as a measure of interference resolution. An independent t-test was used to compare interference resolution between younger and older adults and a median split in older adults was used to compare patterns observed in the PET data between fast and slow older adults.

Study III: Implicit SL in Study III was assessed with the SRTT. In the SRTT, participants saw four rectangles in a horizontal line in the center of the screen. At a rate of one per second, rectangles lit up consecutively and participants were instructed to

Table 2. Sample descriptives on the cognitive battery for each study.

	Study 1 / and 2	Study 3	Study 4
Sample size (sex)	Y = 19 (9 female) / 20 (10 female) O = 18 (9 female) / 20 (10 female)	Y = 14 (10 female) O = 13 (8 female)	Y = 30 (16 female) O = 28 (16 female)
Mean age	Y* = 25.16 (2.27) / 25.20 (2.21) O = 70.33 (3.25) / 70.35 (3.12)	Y* = 24.71 (3.12) O = 68.08 (2.90)	Y* = 25.12 (3.38) O = 67.89 (2.36)
Education in years	Y = 14.61 (2.00) / 14.68 (1.97) O = 14.72 (3.96) / 14.30 (3.97)	Y* = 15.65 (1.72) O = 13.35 (3.01)	Y = 14.80 (2.12) O = 14.67 (3.78)
Processing speed			
Letter comparison (number in 30 sec)	Y* = 9.37 (2.97) / 9.25 (2.94) O = 7.31 (2.23) / 7.43 (2.17)	Y* = 10.14 (3.00) O = 7.81 (3.30)	Y* = 11.02 (2.06) O = 8.46 (2.14)
Pattern comparison (number in 30 sec)	Y* = 21.08 (3.35) / 21.08 (3.26) O = 15.09 (2.48) / 15.37 (2.60)	Y* = 21.86 (2.23) O = 16.23 (3.13)	Y* = 21.95 (2.34) O = 15.83 (2.83)
Digit Symbol	Y* = 36.05 (14.22) / 35.75 (13.90) O = 20.39 (6.14) / 20.30 (5.90)	Not available	Not available
Episodic memory			
Cued word recall (max 18)	Not available	Y* = 13.14 (3.80) O = 8.31 (3.15)	Y* = 12.03 (3.54) O = 7.00 (4.26)
Free word recall (max 16)	Y* = 11.95 (2.37) / 11.90 (2.32) O = 10.06 (2.13) / 9.60 (2.46)	Y* = 10.86 (2.58) O = 7.31 (2.72)	Y* = 10.03 (3.54) O = 7.44 (1.76)
Executive functions			
Task switching			
WCST (Perseverative errors)	Y* = 7.83 (3.73) / 8.00 (3.70) O = 23.44 (13.95) / 24.50 (14.13)	Not available	Not available
WCST (Categories completed)	Y* = 5.94 (0.24) / 5.95 (0.23) O = 4.22 (1.87) / 4.15 (1.95)	Not available	Not available
Plus-Minus task (task switching cost in sec)	Y* = 362 (125)/ 355 (125) O = 476 (143)/ 467 (138)	Not available	Not available
Working memory			
3-back (max 9)	Not available	Y* = 7.02 (1.10) O = 4.90 (2.53)	Y* = 7.08 (1.34) O = 5.04 (1.64)
Language			
Synonym test (number correct)	Not available	Y = 24.86 (3.04) O = 26.92 (2.60)	Y* = 22.57 (3.68) O = 25.96 (2.65)
Letter fluency (generated words)	Y = 17.22 (3.91) / 17.13 (3.82) O = 16.94 (4.29) / 15.55 (4.25)	Not available	Y = 15.05 (4.97) O = 15.89 (4.30)

Note. *significant age-group differences at $p < 0.05$. Y = Younger adults; O = Older adults.
WCST = Wisconsin Card Sorting Task

press one of four buttons (corresponding to rectangles from left to right) whenever a rectangle lit up. The SRTT task lasted for approximately 11 minutes and was administered in a blocked design with 36 sec of task and 6 sec rest between blocks. Unbeknownst to participants, the order in which rectangles lit up followed a repeating 12-item sequence in every other block. The run was split into halves and the increase in RT advantage for sequence blocks (relative to baseline) over time was taken as a measure of implicit SL that was used as a regressor in the fMRI group analysis. Behavioral group statistics were computed using an Age (young/old) x Block type (sequence/baseline) x Half (first/second) ANOVA for RT data. Potential awareness for the repeating sequence was assessed by a questionnaire.

Study IV: In Study IV, participants were assigned to one of two conditions. In the single-task condition, participants performed an SRTT, which closely followed the procedures outlined for Study III. In the dual-task condition, participants also performed an explicit associative binding task concurrent with the SRTT. Three pairs of shapes appeared throughout an SRTT block and participants were asked to remember the pairs; in other blocks, participants were asked to remember one shape only. In between SRTT blocks, a probe appeared. There were two runs of 11 min 25 sec for this task. Groups statistics for implicit SL were computed using an Age (young/old) x Condition (single/dual) x Block type (sequence/baseline) x Run (first/second) ANOVA for the RT data. RT and accuracy data for the probes in the dual-task condition were compared between age groups using an Age (young/old) x Demand (items/pairs) ANOVA. Sequence awareness was assessed using a questionnaire, a generation task (Destrebecqz and Cleeremans, 2001), and a sequence recognition task.

3.3 FUNCTIONAL MAGNETIC RESONANCE IMAGING

MRI is a non-invasive imaging technique that makes use of proton precession under the influence of a strong magnetic field. When radio frequency pulses are applied to the protons that precess parallel to the magnetic field, they absorb energy and temporarily flip from this low-energy state to a high-energy state antiparallel to the magnetic field. As the protons relax back into the low-energy state, the released energy is detected. Gradient coils are used to control the location of proton excitation by separating the imaging field into smaller volumes (voxels), so as to be able to accurately infer spatial location of the transmitted energy. Protons in different tissue types have different relaxation times and therefore generate different signals. Whereas proton excitation and relaxation provide the basis for all MRI scans, variations in scan properties such as flip angle, time between two excitations (repetition time TR) and time between excitation and readout (echo time TE) are used to optimize the imaging of certain tissue types and characteristics.

Neural activation during a given time period can be inferred with fMRI. This type of scan makes use of the fact that the molecule hemoglobin in blood has different magnetic properties depending on whether it carries oxygen. Deoxygenated hemoglobin has shorter relaxation times than oxygenated hemoglobin and therefore fMRI can be used to infer where in the brain oxygenated blood is accumulated (the blood-oxygenation-level dependent or BOLD response). Assuming that increased oxygen supply correlates with neuronal activity, fMRI is used as an indirect measure of dynamic changes in neural activity over time. In task-based fMRI, participants perform a cognitive task during image acquisition so that the researcher can link increases or

decreases in BOLD response to the onset of a stimulus in time. Importantly, the timing of stimuli presentation in an fMRI task is limited by the fact that the BOLD signal change in response to stimulus onset is very slow. The BOLD signal reaches its peak after around 6 sec.

3.3.1 Analysis of fMRI data

In all studies that use fMRI in this thesis, BOLD data were acquired over a period of several minutes while participants performed the cognitive tasks described in the previous section.

fMRI sequences. For Studies I and III, fMRI images were acquired on a 1.5 Tesla General Electrics Signa Excite system with an echo-planar imaging sequence (TR = 2.5 sec, TE = 40 ms, flip angle = 90°, slice thickness 4mm with 0.5 gap, acquired interleaved. Field of View = 220 mm). For Study IV, data were collected on a 3.0 T Siemens Magnetom Trio Tim scanner with a similar sequence (TR = 2.5 sec, TE = 40 ms, flip angle = 90°, slice thickness 3mm, acquired interleaved, Field of View = 230 mm). In all studies, a structural scan was used for co-registration with the functional data.

Pre-processing. Before linking the BOLD signal to the cognitive task, several pre-processing steps were applied to de-noise the data. For all studies, images were skull-stripped, and the time-series data motion-corrected, spatially smoothed, and scaled to a grand mean. Data were high-pass filtered to remove low frequency noise. All pre-processing was performed using automated tools as implemented in FSL (http://www.fmrib.ox.ac.uk/fsl/).

Statistics. The fMRI analyses in all studies were based on General Linear Modeling (GLM). GLM-based fMRI analysis estimates the fit of each voxel´s time-series data to a time-series model. The model typically contains regressors for each of the conditions in the cognitive task. Regressors are derived based on stimulus on-and offsets convolved with a function that approximates the hemodynamic lag. Contrasts are set up to generate activation maps across the whole brain. A statistic is assigned to each voxel indicating how well its time series fits the model time series based on the comparison of one experimental condition (e.g., WM task) to another (e.g., looking at a fixation cross). For Study I, connectivity maps were generated. Here, the regressor of interest is the time series of one region of interest. Therefore, the activation maps reflect how well one regional time series fits another. For Studies I and IV, in addition to the regressors of interest, several nuisance variables were included to remove artifactual signal. These were motion parameters and the signal of white matter, cerebrospinal fluid and global signal. The statistical threshold for group statistics was set at $p < 0.05$ for Study III and at $p < 0.01$ for Studies I and IV. Correction for multiple comparisons was applied at the cluster level in Study I. In Study IV the search volume was restricted to the striatum and MTL by pre-threshold masking.

3.4 POSITRON EMISSION TOMOGRAPHY

A brief introduction to PET has been given in section 1.2.3. PET is a minimally-invasive imaging technique that was used for estimation of D1 receptor densities using [^{11}C]SCH23390 as a ligand in Studies I and II. 300 MBq of the ligand were injected

into the left antecubital vein. Emission data were recorded over a period of 51 minutes in 13 frames of increasing duration after a transmission measurement of 10 min.

3.4.1 Analysis of PET data

Regional radioactivity was plotted for each frame, corrected for decay, and plotted versus time for each regions of interest (ROI) and the reference region cerebellum. An example of TACs is shown below (Figure 5). In Study II (supplementary Figure), time of peak was compared between age groups to ensure that peak and general shape of the TAC did not differ between groups.
The simplified reference tissue model (SRTM) was fitted to TACs to estimate BP of the ligand for each region of interest. The SRTM is a compartmental kinetic model that has been validated for [^{11}C]SCH23390 (Lammertsma and Hume, 1991). For Study I, only BPs of bilateral caudate were used. For Study II, BPs were estimated for several ROIs in striatum and cortex that were manually delineated on T1-weighted MRI images and segmented (grey matter, white matter, cerebrospinal fluid) before TAC derivation.

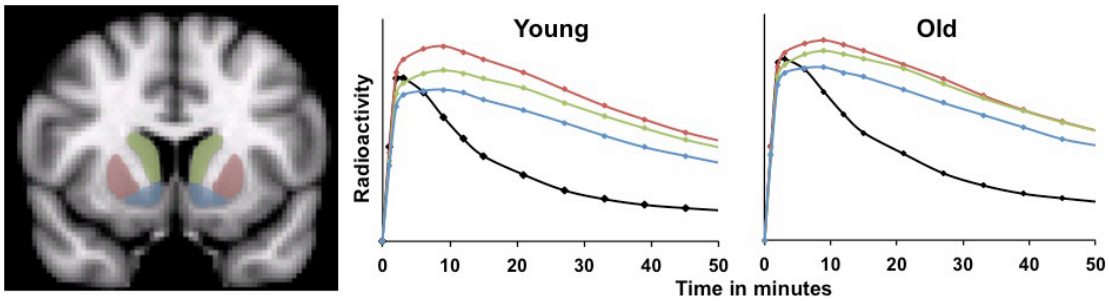

Figure 5. Time-activity curves. Radioactivity plotted against time for sensorimotor striatum (red), associative striatum (green), ventral striatum (blue) and cerebellum (black) for younger and older adults. Data are based on the sample used in Study II.

4 RESULTS

4.1 STUDY I

Several studies have suggested a role for age-related DA changes as a mediator of deficits in executive functioning and episodic memory in older adults (reviewed in section 1.3). Very little is known about the role DA may play in age-related changes in connectivity of cortical networks important for executive functioning, although it has long been established that striatal DA has important modulatory functions in cortico-striato-thalamo-cortical pathways. Study I investigated the association between caudate DA D1 receptor density and functional connectivity in the executive fronto-parietal network and the DMN in younger and older adults during a WM task. Older adults showed reduced caudate D1 receptor density, reduced connectivity between frontal and parietal cortex in the fronto-parietal network, reduced connectivity between medial PFC and posterior cingulate in the DMN, and reduced anti-correlations between the two networks. Importantly, greater caudate D1 receptor density was related to greater connectivity in the fronto-parietal network and stronger anticorrelations between medial PFC and parietal cortex after partialling out the effects of chronological age (Figure 6). D1 receptor densities were not associated with age-related connectivity differences in the DMN. Consistent with some previous reports, older adults showed increased bilateral connectivity of the right PFC to medial and left frontal areas. Increased connectivity within PFC in older adults was positively related to performance on the WM task, but there were no significant correlations between connectivity within PFC and caudate D1 receptor density.

4.2 STUDY II

Age-related decline in striatal DA functions is well documented. Comparatively little is known about age-related DA changes in cortex and it is unclear whether striatal and cortical DA changes in aging are of similar magnitude and whether not they are correlated. Study II estimated age-related reductions in the striatum (associative, sensorimotor, and ventral compartments) and in several frontal areas, the parietal cortex, and the medial temporal lobe.

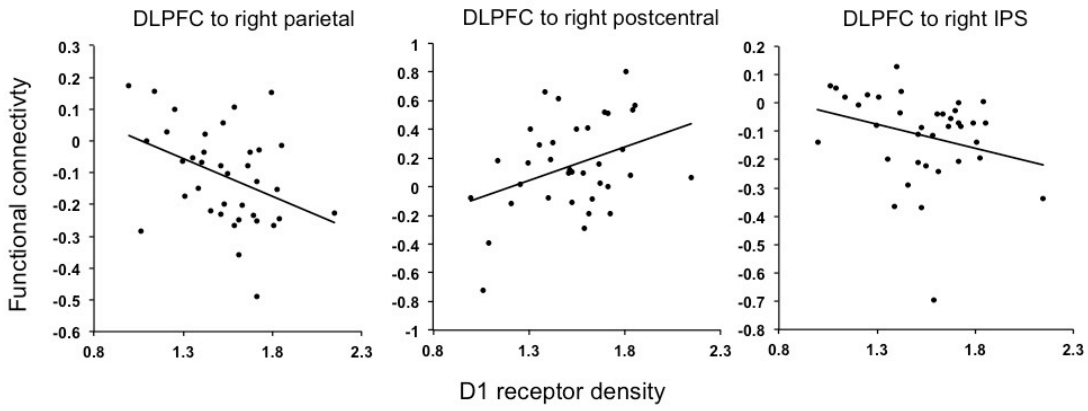

Figure 6. Key finding in Study I: Caudate D1 receptor density is associated with fronto-parietal connectivity after partialling out age (Adapted from Study I).

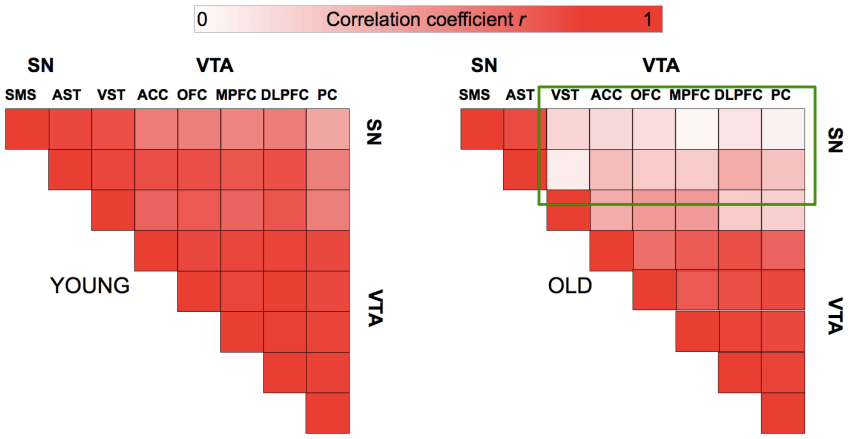

Figure 7. Key finding in Study II: Correlations of D1 receptor densities in areas of the nigrostriatal pathway (innervated by substantia nigra SN) to areas in the mesocortical and mesolimbic pathways (innervated by ventral tegmental area VTA) are reduced in older adults (Adapted from Study II).

Throughout all ROIs, mean losses of D1 receptor density of around 20 % were observed for older, compared to younger, adults. Correlations among all regions of interest showed that D1 receptor densities among areas innervated by the same DA pathway were highly correlated in both younger and older adults. Correlations of receptor densities between pathways, however, were reduced in older adults (Figure 7). This suggests that individual differences in D1 receptor losses in aging do not generalize across DA pathways. Importantly, reduced between-pathway correlations were linked to slower cognitive interference resolution in the older group, suggesting that an imbalance in DA functioning between pathways may contribute to older adults' deficits in executive functioning.

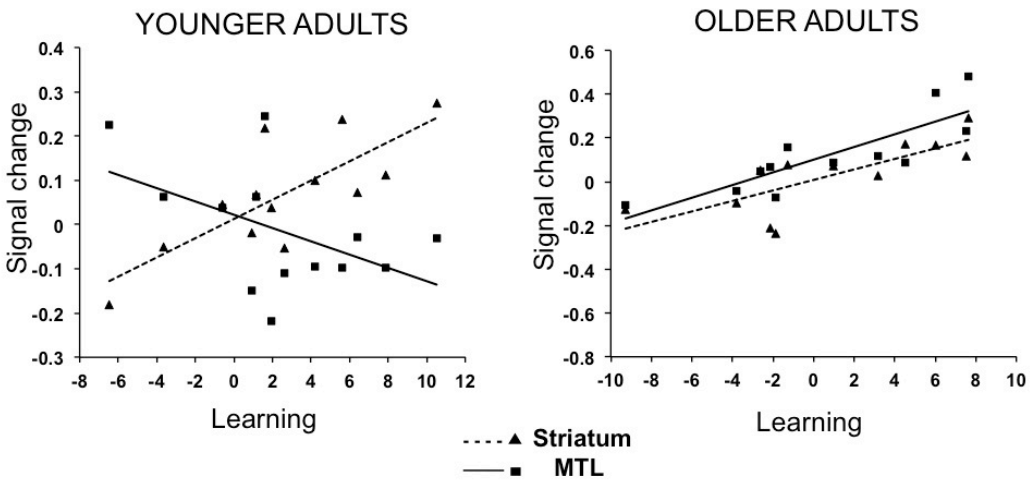

Figure 8. Key finding from Study III: Striatal activity is positively related to SL in younger and older adults alike. MTL activity is negatively related to SL in younger adults, but positively to SL in older adults (Adapted from Study III)

4.3 STUDY III

Study III investigated neural correlates of implicit SL in younger and older adults. SL involves a subcortical-cortical network in which the striatum and DA are key components. Despite age-related changes in striatal functions, SL remains relatively spared in older adults. In Study III, SL was assessed using the SRTT and SL was operationalized as the increase in RT advantage for sequence compared to random blocks over time. Successful SL in younger adults was associated with increasing recruitment of the striatum over time, but decreasing activation of the right parahippocampal gyrus. In older adults, the striatal pattern paralleled the findings in younger adults. Of chief interest, however, for older adults better learning was also related to increasing activation of the right parahippocampal gyrus (Figure 8). These results are consistent with the view that the MTL is disengaged from the task as the striatum is recruited for younger adults. In older adults, both systems are "kept online" to facilitate task performance. In this way, MTL recruitment in older adults may serve compensation. The findings of age-related increases of MTL activation during SL were also later replicated in another study (Dennis and Cabeza, 2010).

4.4 STUDY IV

Study IV follows up on Study III and explores whether the recruitment of right MTL in older adults during SL can in fact be interpreted as compensatory recruitment. According to the hypothesis that the MTL is disengaged from task performance in younger adults but is necessary for SL in older adults, it was predicted that an MTL-taxing secondary task should interfere with SL in older, but not younger adults. The behavioral patterns of a dual SRTT were in accordance with these predictions (Figure 9A). Importantly, the different effect of the secondary task on SL in younger and older adults was reflected not only in performance, but also in activation patterns of the right parahippocampal gyrus (Figure 9B). Younger adults showed greater recruitment of this area during SL under dual-task conditions, consistent with the notion that the right MTL is not necessary for SL and can therefore be engaged in the secondary task. In older adults, the right MTL was recruited during SL under single-task conditions, replicating the findings from Study III. Under dual-task conditions, performance of the

secondary task was associated with greater recruitment of the right MTL during baseline compared to sequence blocks, resulting in a negative parameter estimate for the SL contrast. This pattern is consistent with the notion that the right MTL is involved in SL in older adults. The effect of dual-task requirements on activation in right MTL was restricted to early SL. In a second run of the task, no effects were found in MTL and there was an improvement in SL across runs for all groups, suggesting that the right MTL is particularly important to SL in older adults early on in learning.

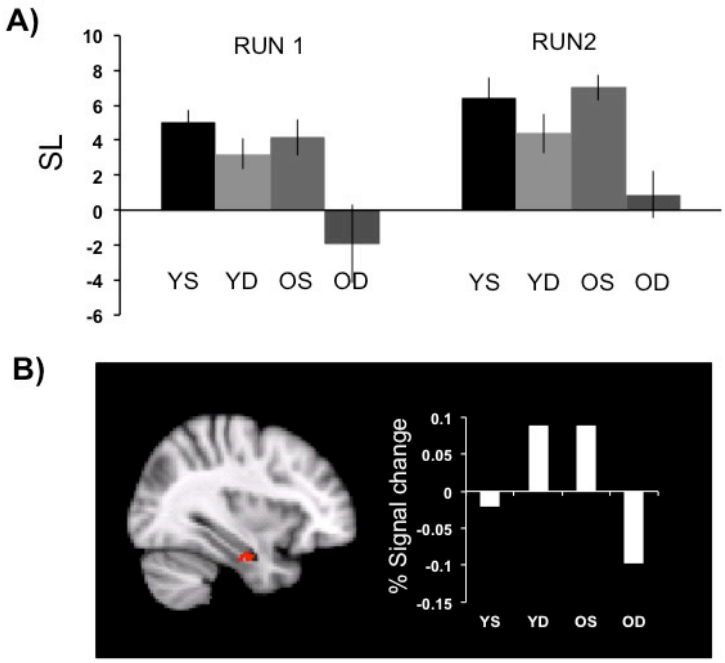

Figure 9. Key findings from Study IV: A) A secondary task selectively interrupts SL in older adults. B) Differential effects of task condition (single S/ dual task D) on SL in younger (Y) and older adults (O) is also reflected in right anterior parahippocampal gyrus BOLD activity.

5 DISCUSSION

5.1 SUMMARY OF FINDINGS

This thesis investigates the neural basis of executive functioning and implicit learning in adulthood and aging using a combination of fMRI and DA PET. Two studies sought to determine the role of age-related changes in DA in older adults' deficits in executive functioning: In Study I, age-related decline in caudate D1 receptor density was associated with reduced connectivity between DLPFC and parietal cortex within a fronto-parietal network, and reduced anticorrelations of the medial PFC to parietal areas. The association between striatal DA receptors and fronto-parietal connectivity independent of chronological age is in concordance with a modulatory role of striatal DA in cortico-striato-thalamo-cortical pathways involved in cognition. This suggests that losses of striatal DA functions may mediate some of the age-related deficits in functional network integrity related to executive functions.

Study II explored the association between age-related changes in D1 receptor densities in striatum and cortex. It was found that, although age-related decline in striatum and cortex are of similar magnitude, they are not correlated. This suggests that age effects on the meso-cortico-limbic pathways and the nigrostriatal pathway occur relatively independent of each other. Importantly, reduced correlations between pathways were related to slower cognitive interference resolution. This supports the conclusion that an imbalance between pathways (i.e., accelerated DA losses in one compared to the other pathway) is related to deficits in executive functioning in aging.

Study III and IV investigated the neural basis of implicit learning in aging using fMRI and the SRTT, a classic implicit SL task. Implicit learning is relatively spared in aging, despite the fact that this form of learning is strongly linked to striatal functioning and the DA system. In this way, the "correlative triad" of aging, DA, and cognition does not hold for the case of implicit learning. In Study III, it was shown that SL is associated with striatal activation and MTL deactivation in younger adults. In older adults, however, SL was related to activation of both striatum and MTL. Study IV showed that when a secondary task, designed to tax associative binding and the MTL, was performed concurrently with the SRTT, only older adults showed a deficit in SL. Moreover, an interaction between task condition (single vs dual task) and age group was found in activation of the right MTL. The area in the right MTL that was disengaged in younger adults, but engaged during SL in older adults, and where age-differential effects of the secondary task were found, converge on the right anterior parahippocampal gyrus. Collectively, the findings from Studies III and IV suggest that recruitment of the right MTL in older adults may be compensatory and contribute to the relative preservation of implicit SL in aging.

5.2 THE ROLE OF DOPAMINE IN COGNITIVE AGING

The correlative triad of aging, DA and cognition suggests that age-related cognitive changes are partly mediated by DA losses (Bäckman et al., 2006; 2010). Thus far, experimental studies in humans that have sought confirmation for the correlative triad have been largely descriptive. Associations of executive functioning and episodic memory to DA functioning were found after partialling out the effects of age (e.g.,

Volkow et al., 1998; Bäckman et al., 2000; Erixon-Lindroth et al., 2005). Similarly, recent studies have identified age-independent associations between brain activity and DA functioning (Fischer et al., 2010; Morcom et al., 2009; Bäckman et al., 2011). Study I extends these findings to suggest a mechanism by which age-related changes in striatal D1 receptors may contribute to deficits in executive functioning. The finding that caudate DA receptor density was associated with decreased integrity of fronto-parietal connectivity is consistent with the view of striatal DA as a critical modulator of cortico-cortical pathways via striatum and thalamus (e.g. Alexander et al., 1986; Kimura and Graybiel, 1995; Joel and Weiner, 1994; 2000). Of particular relevance to executive functioning is the associative loop. Association cortices (prefrontal and parietal areas) project to the caudate nuclei from which direct and indirect pathways connect to thalamus and back to cortex (Figure 2). The direct and indirect pathways of this circuitry work antagonistically and the modulatory role of striatal DA is exerted by balancing excitatory and inhibitory activity of these two pathways. In this way, striatal DA may gate input from association areas, channel information processing of salient stimuli, and inhibit distracting or irrelevant stimuli.

Dopaminergic innervation of striatum and cortex proceeds via midbrain pathways originating from the SNc and VTA, respectively. The precise roles of striatal and cortical DA in cognitive functioning have yet to be identified. Recently, theories have been proposed suggesting a role for striatal DA in "cognitive flexibility", consistent with the modulatory role of striatal DA in cortico-cortical connectivity described above, whereas cortical DA may be more related to "cognitive stability" (Cools, 2008). Independent, but complementary, roles of striatal and cortical DA in cognitive functioning are consistent with the findings of Study II. This study showed that areas innervated by the SNc and areas innervated by the VTA age independently, as there were weak correlations between striatal and cortical D1 receptor densities in older adults. Moreover, an age-related imbalance between the striatal pathway and the mesocortical pathway was related to slower cognitive interference resolution. In line with animal studies (e.g., Haber et al., 2000), Study II suggests that, although cortical and striatal DA innervation proceeds via independent pathways, information transfer between pathways is important for executive tasks and processing speed in which both striatal and cortical DA play important roles.

The finding of an age-related segregation of DA pathways is also interesting in relation to studies of Parkinson's disease and schizophrenia. Symptoms of Parkinson's disease are primarily disturbances in movement, but deficits of executive functioning are also frequently observed (e.g., Owen et al., 1992; Lewis et al., 2003). Schizophrenia is a psychiatric disorder characterized by hallucination and intrusive thoughts. Cognitive disturbances in schizophrenia are pronounced for executive functions (Weinberger and Gallhofer, 1997; Eisenberg and Bergman, 2010). Deficits in switching ability, WM and inhibitory functions have been shown for both Parkinson's disease (e.g., Alevriadou et al., 1999; Bruck et al., 2001; Lewis et al., 2003) and schizophrenia (e.g., Buchanan et al., 1994; Koren et al., 1998; Callicott et al., 2003). In one study that directly compared cognitive performance between schizophrenics, patients with Parkinson's disease, patient with medial-temporal lesions and healthy controls, it was confirmed that the patterns of executive dysfunction were quite similar for schizophrenia and Parkinson's disease. Both patient groups showed reduced performance on several tests of executive functioning compared to healthy controls and patients with lesions of the temporal lobe (Pantelis et al., 1997). In Parkinson's disease, neuronal cell death takes place in SNc, whereas VTA remains largely spared (Fearnley and Lees, 1991). This leads to striatal DA hypofunction whereas cortical DA levels remain normal, at least in earlier stages of

the disease (see Smith and Villalba, 2008, for review). One working hypothesis for schizophrenia is that nigrostriatal DA release is increased compared to healthy controls, whereas frontal lobe functioning is reduced (Knable and Weinberger 1997; Laruelle et al., 1999; Stone et al., 2007). Thus, despite quite different dysregulation of the DA system in the two disorders, deficits in executive functions are very similar. Taken together, these findings and the results from Study II could suggest that a general imbalance between cortical and striatal DA functioning, independent of direction, may be core to deficits in executive functioning.

5.3 COMPETITION AND COMPENSATION

In the preceding section, it was suggested that the striatum has a modulatory role in gating PFC input in response to external stimuli. Consistent with this view, the striatum is important for stimulus-response (S-R) learning, where gradual, albeit unconscious, S-R associations are formed in response to recurring or rewarded stimuli. The role of the striatum in S-R learning has been shown in many animal studies and in fMRI studies in humans (see Packard and Knowlton, 2002; Packard, 2009; Rieckmann and Bäckman, 2009, for reviews). Pertaining to Studies III and IV, it has been suggested that striatal-based S-R learning proceeds independently of MTL-based flexible association formation between stimuli (stimulus-stimulus learning S-S) (e.g., Poldrack et al., 2001). The dissociation of striatal and MTL-based learning, and the notion that they may work in competition, was first identified in rat studies using water-maze tasks (Packard and Knowlton, 2002). Lesion studies in rats have shown that the striatum mediates simple response learning (i.e., learning that a certain sequence of turns will lead to reward), whereas the MTL mediates flexible place learning (i.e., learning the location of reward independent of starting position). Most interestingly, when one region is lesioned, learning switches to the other system (Lee et al., 2008), supporting the notion that one system can take over when the other is impaired.

Whereas compensation has been observed in animals in both directions, the literature in humans is limited to observations of increased reliance on the MTL when the striatum is impaired (Dagher et al., 2001; Moody et al., 2004; Voermans et al., 2004; Beauchamp et al., 2008), but not the reverse. Study III suggests that reliance on the MTL during the SRTT in older adults was associated with better SL. In younger adults however, MTL deactivation and striatal activation was related to SL. These data are consistent with the idea of competing brain systems that may co-operate when the striatal system is impaired and extend findings from patient studies to healthy aging. As described in the preceding sections, input to the striatum comes largely from the frontal cortex. The PFC is also tightly coupled to the MTL via the entorhinal cortex. The enthorinal cortex receives input from the PFC and projects to the hippocampus. With PFC output reaching striatum, MTL, and also other cortical areas directly, the PFC may be critical to regulating competition (suppressing activation of one area while recruiting another) and compensation (enhancing recruitment of one pathway when another is impaired) (e.g., Miller and Cohen, 2001; Poldrack and Packard 2003).
An important caveat of Study III is that studies of implicit SL in the experimental setting may not generalize to everyday life. Although implicit acquisition of sequences and regularities in the environment through cortico-striatal pathways is at the core of cognition, multiple cognitive operations are performed simultaneously in natural settings. In fact, automatic and routine-like behavior that proceeds without conscious awareness allows us to perform several behaviors in parallel, such as walking to work or driving a car whilst talking to a friend. A key implication of the data from Study III,

that older adults need to keep the MTL "online" during simple incremental learning, is that performance of concurrent tasks which involve the MTL may be limited by dual load on the MTL. Using a dual-task design, Study IV showed that this was the case and therefore demonstrates the cost of compensation: When a secondary task required the MTL at the same time as the SL task, SL failed in older adults. The scenario of Study IV, performance of two operations in parallel, is much more similar to everyday life than mere performance of a repetitive motor task. This suggests that although SL is spared in older adults in the laboratory, this may not generalize to everyday life.

Finally, discussion of competition and compensation between brain systems is by no means restricted to striatum and MTL and also pertain to results of Study I. In a landmark review paper, Miller and Cohen (2001) likened the PFC to a "switch operator in a system of railroad tracks" (p. 184). The analogue refers to the ability of the PFC to modulate and orchestrate information processing along several pathways in a top-down fashion. Study I yielded several findings that are consistent with a "switch operator" function of the PFC: (1) Fronto-parietal connectivity was negatively correlated with bilateral prefrontal activity, suggesting that when fronto-parietal pathways are engaged, fronto-frontal pathways are less so and vice versa. (2) Fronto-parietal connectivity was related to caudate DA receptor density, but fronto-frontal connectivity was not. This supports the existence of a fronto-parietal pathway via the striatum, which is functionally different from direct fronto-frontal pathways. (3) Fronto-frontal connectivity was beneficial to performance in older adults, who had reduced fronto-parietal connectivity associated with decreased striatal DA functioning.

These findings suggest a role for the PFC in selecting direct fronto-frontal pathways over fronto-parietal pathways via striatum when striatal DA receptor losses are present. This view is consistent with the notion of hemispheric asymmetry reduction in older adults (HAROLD) (Cabeza, 2002) and the view that greater bilateral PFC activation in older adults may be compensatory. However, a recent longitudinal study of 38 older adults showed that age-related increases in frontal bilaterality were observed in a cross-sectional comparison, but a longitudinal comparison of the same sample over 6 years exclusively revealed decreasing frontal activations (Nyberg et al., 2010). This may suggest that cross-sectional comparisons may be biased toward high-performing older adults, which could explain over-recruitment (Nyberg et al., 2010) and highlights the need for longitudinal research to corroborate cross-sectional findings.

5.4 CLINICAL SIGNIFICANCE

The studies in this thesis explore the neural mechanisms underlying cognitive changes in old age. Ultimately, understanding brain changes in clinically normal older adults will aid the differentiation of healthy aging from neuropathological processes, which in turn may have implications for the development of intervention strategies.

Although the translation from basic research to clinical intervention is non-trivial, the studies in this thesis may have clinical implications. For example, Study I and II confirm that age-related changes in the DA system may in part mediate executive dysfunction in older adults. However, Study II also suggests that the relation between DA and executive functioning in humans is complex. If one envisions the development of intervention strategies in older adults that target the DA system, Study II suggests that administration of a DA agonist is not a sensitive enough approach. A global DA agonist would likely lead to overdosing of one compared to another DA pathway, as

DA losses in aging do not necessarily generalize across pathways. Even though this message might appear negative, it is important to delineate which interventions in aging may not be worthwhile.

Study III and IV also hold possible implications for clinical practice. These studies suggest that compensatory neural reorganization might explain why deficits in implicit learning in older adults are small. These results converge with studies in Parkinson's disease and Huntington's disease to suggest that the MTL may be involved in compensation in the presence of striatal losses. From a clinical standpoint, compensatory processes may "mask" subtle behavioral signs that could indicate striatal dysfunction. Indeed, in Parkinson's disease behavioral symptoms typically occur only after around 80 % of dopaminergic neurons have died (Fearnley and Lees, 1991), suggesting the presence of compensatory processes in early stages of the disease (Bezard et al., 2003). Study IV suggests that cognitive tests, which target specific compensatory processes (in this case recruitment of the MTL), could reveal cognitive deficits that would otherwise not be apparent.

5.5 METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS

5.5.1 fMRI

Minimally invasive neuroimaging methods in humans have contributed greatly to our understanding of neural correlates of cognition. However, functional and molecular imaging methods in humans are not without shortcomings and pitfalls and this thesis would be incomplete without acknowledging some of the possible problems with these methods. Over the last 20 years, fMRI has quickly developed to be the primary imaging technique in cognitive neuroscience. Along with its great popularity, several lines of critique have recently been voiced regarding its usefulness (Vul et al., 2009; Gonsalves and Cohen, 2010; Poldrack, 2010). Much of the controversies surrounding fMRI relate to analytic strategies, and specifically to the use of unreliable statistics. As described in the Methods section, whole-brain analyses of fMRI data search for "active" regions of the brain across tens of thousands of voxels. Yet, statistics often do not rigorously control for multiple comparisons. Uncorrected statistics have rightly been criticized for inflating the rate of falsely active voxels and results from uncorrected statistics should be viewed cautiously.

However, equally important to sound statistics is consideration of the framework in which a particular study is set. For example, in Study I, all areas where age differences in cortical connectivity were present were used as ROIs. There were no a-priori hypotheses about which cortical connections may be associated with DA and which may not. Because of the explorative nature of the analyses, a conservatively corrected statistical threshold was chosen so as to increase the likelihood of finding only highly reliable age differences in connectivity. The framework for Study III and IV was quite different. Here, specific hypotheses were laid out about the involvement of striatum and MTL in SL based on previous findings in patients and from animal research. Therefore, in contrast to the exploratory nature of Study I, these studies are more confirmative in nature, which might justify the use of a lower statistical threshold.

Another major criticism of fMRI as a research method is its descriptive nature. Although fMRI has the ability to signal which regions or networks of the brain are involved in a particular cognitive process, the underlying neural mechanisms remain

largely unknown. It is therefore of utmost importance for the future of cognitive neuroscience to combine fMRI with other imaging methodologies like molecular imaging, electroencephalography and magnetoencephalography, or with in vivo recordings in animals, in order to gain insights into the neuronal properties and synaptic mechanisms related to fMRI activations. An alternative to multi-modal techniques may also be the utilization of other fMRI-based parameters. Specifically, cerebral blood flow CBF and cerebral metabolic rate of oxygen CMRO2 can be used to obtain information about the physiological mechanisms underlying the BOLD signal (Ances et al., 2009; Hutchison et al., submitted manuscript).

5.5.2 Selectivity of PET ligands

PET is often praised for being a more direct imaging method compared to MRI and imaging of specific proteins in living humans is to date feasible only with PET. The major limitation of PET, however, is the scarcity of suitable ligands. In Studies I and II, [^{11}C]SCH23390 was used for quantification of D1 receptor density. [^{11}C]SCH23390 is widely used for PET imaging of D1 receptors. As demonstrated in Study II, one of the major advantages of this tracer is that it is sensitive to D1 receptors in striatum and cortex alike. However, as is the problem with a number of other ligands of the DA system, [^{11}C]SCH23390 also has some affinity for serotonin receptors (5-HT2A). Earlier studies suggested that affinity for 5HT2A receptors is around 10 times lower than that for D1 receptors (Hicks et al., 1984; Taylor et al., 1991; Alburges et al., 1992). However, a more recent study suggested that up to 25 % of [^{11}C]SCH23390 may be due to 5-HT2A binding (Ekelund et al., 2007). 5-HT2A receptors are found in cortex but are largely devoid in striatum and age-related losses of cortical 5-HT2A receptors have been demonstrated (Rosier et al., 1996). As described in Study II, a number of observations suggested that confounding effects of 5-HT2A binding are most likely small. First and foremost, striatal and cortical BPs were highly correlated in younger adults indicating that BP in striatum and cortex does not reflect binding to different receptor types. That said, studies using [^{11}C]SCH23390 and other markers of the DA system with moderate selectivity should always consider effects of binding to markers of the serotonin system as a potentially confounding effect.

5.5.3 Narrow age groups

The last methodological consideration relates not to the imaging techniques themselves, but to the use of an extreme age groups design, which was adopted in all four studies. Because of the high cost and technical difficulties associated with functional and molecular neuroimaging, age-comparative studies often rely on comparing a group of younger adults in their 20s to older adults in their 60s and 70s. This approach has several disadvantages. Observed differences between age groups cannot provide any information about the shape of the association with age across the adult lifespan. Many age-related brain changes do not follow a linear trend. Volume reductions of the hippocampus as well as white matter volume losses, for example, consistently show nonlinear associations with age across the adult life span (e.g., Good et al., 2001; Raz et al., 2005). Age comparisons between narrow age groups are insensitive to such associations and therefore provide a rather crude estimation of age-related changes in brain and cognition. Toward this end, studies of individuals covering the entire adult age range would be desirable.

Another limitation of cross-sectional comparisons between age groups is that they can merely demonstrate associations, but not causality. Recently, longitudinal neuroimaging studies have emerged. Relating to the findings in Study 1, a cross-sectional comparison revealed over-recruitment of PFC in old age, but a longitudinal

comparison revealed exclusively decreases in frontal-cortex activity across time (Nyberg et al., 2010). This suggests that cross-sectional comparisons might reveal spurious age effects that could be due to sample selection. In study I, a negative relation between fronto-parietal connectivity and bilaterality in frontal connectivity across the whole sample could indeed suggest that individuals may be intrinsically either unilateral frontal-parietal (related to DAergic mechanisms) or bilateral-frontal (not related to DAergic mechanisms), possibly due to differences in acquired strategies and/or genetic influences. Thus, it is conceivable that in younger adults the fronto-parietal system and the bilateral-frontal system are equally efficient and indistinguishable in terms of their relation to task performance. The fronto-parietal system may, however, be more susceptible to age-related processes (perhaps because of its vulnerability to age-related DA losses), which may lead to biased sampling towards well-performing bilateral-frontal older adults.

On the other hand, relating to Study III and IV, a longitudinal study in Parkinson's disease has provided support for neural reorganization and the interpretation that the MTL may be recruited during SL when the striatum is impaired (Carbon et al., 2010). Performance on a motor sequencing task during PET measurement of cerebral blood flow was assessed in thirteen patients with Parkinson's disease over two years. Only those patients that maintained performance showed increased blood flow in right hippocampus and parahippocampal gyrus during motor sequencing over two years. This supports cross-sectional findings of increased reliance on the MTL in patients with Parkinson's disease and indicates that these effects are likely not the effect of biased sampling, but do in fact reflect neural reorganization.

5.6 CONCLUSIONS AND AVENUES FOR FUTURE RESEARCH

This thesis included four studies that explored neural correlates of executive functioning and implicit learning in aging. Study I contributed to the existing literature on human aging, DA, and executive functioning to show that age-related changes in striatal DA D1 receptors are associated with reduced fronto-parietal connectivity. Study II showed that age-related losses of D1 receptors in striatum and cortex proceed independently, which may contribute to deficits in interference resolution. Studies III and IV explored age-related neural reorganization during implicit SL in older, compared to younger, adults. It was found that older adults rely on the right MTL and striatum during performance of a SL whereas younger adults rely on striatum only. The increased recruitment of MTL in older adults was interpreted as compensation.

Future studies on the role of DA in cognitive aging should be designed to go beyond mere associations among the three entities, aging, DA, and cognition. Three interesting avenues for future research are outlined in the following: (1) As discussed above, longitudinal studies are needed to support findings from cross-sectional associations in order to be able to infer causal relationships between age-related changes in DA functioning and deficits in executive functions. Relatedly, longitudinal research will be important to identifying a dopaminergic "cascade" of cognitive aging in which some effects (e.g. decreases in functional connectivity) may precede effects on performance in a causal chain; (2) Research on the role of DA in cognitive aging should strive to include other markers of neurobiological changes. In the literature on the cognitive neuroscience of aging, single markers such as white-matter changes, grey matter volume changes, neurotransmitter losses and amyloid accumulation are all frequently discussed as mediators of age-related deficits in cognitive performance and brain

activity. With multi-modal imaging strategies becoming more and more available, an important avenue for future research will be to disentangle the different contributions of various age-related neurobiological changes to cognitive functioning within individuals. (3) Finally, as has become apparent in various places throughout the thesis, the precise role of DA in cognition and the differential contributions of striatal and frontal DA are still largely unknown. To describe how age-related change in DA functioning may mediate cognitive decline more precisely, it would be useful to include other human models of altered DA functions, such as Parkinson's disease or schizophrenia, to corroborate the findings of age-comparative studies.

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Zhu, D. C., Zacks, R. T., & Slade, J. M. (2010). Brain activation during interference resolution in young and older adults: an fMRI study. *Neuroimage, 50*, 810-817.

8 APPENDIX

List of dissertations from the Aging Research Center and the Stockholm Gerontology Research Center, 1991-2008

1991
Herlitz Agneta. Remembering in Alzheimer's disease. Utilization of cognitive support.

1992
Borell Lena. The activity life of persons with a dementia disease.

1993
Fratiglioni Laura. Epidemiology of Alzheimer´s disease. Issues of etiology and validity.
Almkvist Ove. Alzheimer´s disease and related dementiadisorders: Neuropsychological identification, differentiation, and progression.
Basun Hans. Biological markers in Alzheimer´s disease. Diagnostic implications.

1994
Grafström Margareta. The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)
Holmén Karin. Loneliness among elderly - Implications for those with cognitive impairment. (Umeå University)
Josephsson Staffan. Everyday activities as meeting-places in dementia.
Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.
Forsell Yvonne. Depression and dementia in the elderly.

1995
Mattiasson Anne-Cathrine. Autonomy in nursing home settings.
Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996
Wahlin Åke. Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.
Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)
Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997
Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.
Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person (Licentiate thesis)

1998
Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias.
Guo Zhenchao. Blood pressure and dementia in the very old. An epidemiologic study.
Björk Hassing Linda. Episodic memory functioning in nonagenarians. Effects of

demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)
Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 yeras and above (Licentiate thesis)

1999

Almberg Britt. Family caregivers caring for relatives with dementia – Pre- and post-
Robins Wahlin Tarja-Brita. Cognitive functioning in late senescence. Influences of age and health.
Zhu Li. Cerebrovascular disease and dementia. A population-based study.

2000

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)
von Strauss Eva. Being old in our society: Health, functional status, and effects of research.

2001

Jansson Wallis. Family-based dementia care. Experiences from the perspective of spouses and adult children.
Kabir Nahar Zarina. The emerging elderly population in Bangladesh: Aspects of their health and social situation.
Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.

2002

Fahlander Kjell. Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.
Giron Maria Stella T. The rational use of drugs in a population of very old persons.

2003

Jönsson Linus. Economic evaluation of treatments for Alzheimer's disease.

2004

Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer´s disease
Cornelius Christel. Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project
Qiu Chengxuan. The relation of blood pressure to dementia in the elderly: A community-based longitudinal study
Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.
Larsson Kristina. According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

2005

Derwinger Anna. Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.
De Ronchi Diana. Education and dementing disorders. The role of schooling in dementia and cognitive impairment.
Passare Galina. Drug use and side effects in the elderly. Findings from the Kungsholmen Project.

Jones Sari. Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.
Karp Anita. Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.
Nilsson Jan. Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

2006

Klarin Inga. Drug use in the elderly – are quantity and quality compatible.
Nilsson Erik. Diabetes and cognitive functioning: The role of age and comorbidity.
Ngandu Tiia. Lifestyle-related risk factors in dementia and mild cognitive impairment: A polpulation-based study.
Erika Jonsson Laukka. Cognitive functioning during the transition from normal aging to dementia.

2007

Ferdous Tamanna. Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)
Westerbotn Margareta. Drug use among the very old living in ordinary households-Aspects on well-being, cognitive and functional ability.
Rehnman Jenny. The role of gender in face recognition. (Stockholm University)
Beckman Gyllenstrand Anna. Medication management and patient compliance in old age
Nordberg Gunilla. Formal and informal care in an urban and a rural population. Who? When? What?

2008

Gavazzeni Joachim. Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)
Marengoni Alessandra. Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.
Rovio Suvi. The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.

2009

Atti Anna-Rita. The effect of somatic disorders on brain aging and dementia: Findings from population- based studies.
Livner Åsa. Prospective and retrospective memory in normal and pathological aging.
Paillard-Borg Stephanie. Leisure activities at old age and their influence on dementia development.
Rana M AKM. The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh.
Thilers Petra. The association between steroid hormones and cognitive performance in adulthood.

2010

Fors Stephan. Blood on the tracks. Life-course perspectives on health inequalities in later life.
Keller Lina. Genetics in dementia. Impact of sequence variations for families and populations.

2011

Schön Per. Gender matters. Differences and change in disability and health among our oldest women and men.

Caracciolo Barbara. Cognitive impairment in the nondemented elderly: Occurrence, risk factors, progression.