From AGING RESEARCH CENTER

Karolinska Institutet, Stockholm, Sweden

LIFESTYLE, COGNITIVE AGING, AND BRAIN CORRELATES

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Karolinska Institutet

Stockholm 2017

Published by Karolinska Institutet.
Printed by E-Print AB 2017

ISBN 978-91-7676-689-7

Lifestyle, cognitive aging, and brain correlates

THESIS FOR DOCTORAL DEGREE (Ph.D.)

Thesis defended at Hillarpsalen, Retzius väg 8, Karolinska Institutet, Solna
Tuesday May 23rd 2017 at 1.30 PM

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ABSTRACT

Inter-individual differences in level and rate of cognitive decline typically seen in aging have been linked to inter-individual differences in lifestyle factors such as leisure activities, including physical activity. The general aim of this thesis was to further our understanding of how and why leisure activity engagement is related to aging-related changes in cognitive performance. Specifically, we sought to (a) identify lifestyle components that are associated with late-life cognitive performance, (b) identify brain correlates of these lifestyle components that are also relevant for cognitive performance, and (c) explore the relative importance of lifestyle- and health-related factors for predicting cognitive change, as well as interactive effects among these factors.

In Study I and II, we investigated associations between 3-year changes in leisure activities and concurrent changes in cognitive performance and white matter microstructure in 563 (Study I) and 442 (Study II) participants aged 81 years and older. Study I documented changes in white matter microstructure in the corticospinal (CS) tract to be associated with changes in perceptual speed. In Study II, we observed that concurrent change in frequency of engagement in social activities (e.g. going out to eat in a restaurant, going to the movies, concerts, or the theater) was related to change in both white matter microstructure in the CS tract and in perceptual speed. Change in white matter microstructure in the CS tract statistically accounted for the association between changes in frequency of social leisure activities and perceptual speed.

In Study III, we turned to $D_{2/3}$ dopamine receptor ($D_{2/3}$DR) availability as a potential brain correlate of lifestyle and cognition in aging. We investigated $D_{2/3}$DR availability, cognitive performance, and physical activity in 178 healthy adults aged 64-67 years. Participants completed tests of working memory, episodic memory, and processing speed, and a leisure activity questionnaire. Subjective intensity, but not frequency, across the activities each individual performed was associated with $D_{2/3}$DR availability in caudate nucleus as well as with episodic and working memory. Episodic memory was also related to $D_{2/3}$DR availability in the caudate, forming a correlative triad with physical activity intensity and caudate $D_{2/3}$DR availability.

In Study IV, we applied a new data-mining technique called structural equation modelling trees and forests to investigate the relative

importance of leisure activity engagement, physical activity, and other age- and health-related factors in predicting subsequent 6-year change in perceptual speed in 1046 participants aged 60 years and older. With regard to variable importance, a measure that subsumes main effects and interactions among predictors, frequency of leisure activities was not unimportant, although less important than age, retirement status, walking speed, and multimorbidity. Conceivably, the association between leisure activity engagement and subsequent cognitive decline is conditional upon age- and health-related factors included in the current analyses.

Regarding aim (a), identifying lifestyle components related to cognitive aging, we identified change in social activities to be related to change in perceptual speed (Study II). We also found that subjective intensity, but not frequency, of physical activity was related to episodic and working memory (Study III). Regarding the relative importance of frequency of leisure activity engagement as a predictor of change in cognition, we observed some importance of all types of activities, except for physical activity, in predicting change in perceptual speed (Study IV). Concerning aim (b), identifying brain correlates of lifestyle components and cognitive performance, we observed white matter microstructural changes to be related to changes in both leisure activity and perceptual speed (Study II), and $D_{2/3}$DR availability (Study III) to be related to both subjective physical activity intensity and episodic memory. Regarding aim (c), exploring the relative importance of lifestyle components as predictors of subsequent cognitive decline (Study IV), we found rather small effects of the lifestyle components investigated in Studies II and III, but still found leisure activities to be informative as predictors when using a data-mining approach that takes interactive effects with other predictors into account.

The studies in this thesis contribute with new data on associations between lifestyle and cognitive aging, and on brain measures correlated with these two factors. Specifically, we are the first to show parallel changes in leisure activity, white matter microstructure, and perceptual speed. We are also the first to observe an association between physical activity intensity and $D_{2/3}$DR availability. In sum, the present results indicate that engaging in social activities in very late life and physical activity intensity around retirement age are related to cognitive performance and associated brain parameters. Although the issue of causal directionality remains unresolved, leisure activities are correlates and informative predictors of cognitive decline.

LIST OF SCIENTIFIC PAPERS INCLUDED IN THE THESIS

I. Lövdén, M., **Köhncke, Y.,** Laukka, E. J., Kalpouzos, G., Salami, A., Li, T.-Q., Fratiglioni, L., Bäckman, L. (2014). Changes in perceptual speed and white matter microstructure in the corticospinal tract are associated in very old age. *NeuroImage*, 102(520-30).

II. **Köhncke, Y**., Laukka, E. J., Brehmer, Y., Kalpouzos, G., Li, T.-Q., Fratiglioni, L., Bäckman, L., Lövdén, M. (2016). Three-year changes in leisure activities are associated with concurrent changes in white matter microstructure and perceptual speed in individuals aged 80 years and older. *Neurobiology of Aging*, 41, 173-186.

III. **Köhncke, Y.,** Papenberg, G. Jonasson, L., Karalija, N., Wåhlin, A., Salami, A., Andersson, M., Axelsson, J. E., Nyberg, L., Riklund, K., Bäckman, L., Lindenberger, U., Lövdén M. (under revision): Self-rated intensity of habitual physical activities is positively associated with dopamine D2/3 receptor availability and cognition.

IV. **Köhncke, Y.,** Laukka, E. J., Wang, H. X., Wang, R., Ferencz, B., Papenberg, G., Santoni, G., Calderón-Larañaga, A., Welmer, A.-K., Fratiglioni, L., Lindenberger, U., Bäckman, L., Lövdén, M., Brandmaier, A. M., (Manuscript): The relative importance and interactive patterns of predictors of aging-related decline in perceptual speed.

ADDITIONAL SCIENTIFIC PAPERS, NOT INCLUDED IN THE THESIS

I. Papenberg, G., Lövdén, M., Laukka, E. J., Kalpouzos, G., Keller, L., Graff, C., **Köhncke, Y.,** Li, T.-Q., Fratiglioni, L., Bäckman, L. (2014). Magnified effects of the COMT gene on white-matter microstructure in very old age. *Brain Structure and Function*, 1-12.

II. Werheid, K., **Köhncke, Y.,** Ziegler, M., & Kurz, A. (2015). Latent change score modeling as a method for analyzing the antidepressant effect of a psychosocial intervention in Alzheimer's disease. *Psychotherapy and Psychosomatics*, 84(3), 159-166.

III. Nyberg, L., Karalija, N., Salami, A., Andersson, M., Wahlin, A., Kaboovand, N., **Köhncke, Y.,** Axelsson, J. E., Rieckmann, A., Papenberg, G., Garrett., D. Riklund, K., Lövdén, M., Lindenberger, U., Bäckman, L. (2016). Dopamine D2 receptor availability is linked to hippocampal-caudate functional connectivity and episodic memory. *Proceedings of the National Academy of Sciences of the United States of America*, 113(28), 7918-7923.

CONTENTS

LIST OF ABBREVIATIONS

ApoE E4	Apolipoprotein E polymorphism, allele E4 (rs7412-C, rs429358-C)
BP_{ND}	Binding potential to non-displaceable tissue
CFA	Confirmatory factor analysis
CCG	Cingulate gyrus part of cingulum
CS	Corticospinal tract
DA	Dopamine
DTI	Diffusion-tensor imaging
$D_{2/3}$DR	$D_{2/3}$ dopamine receptor
FA	Fractional anisotropy
FMAJ	Forceps major
FMIN	Forceps minor
IFOF	Inferior fronto-occipital fasciculus
LCM	Latent change score model
MD	Mean diffusivity
MRI	Magnetic resonance imaging
ROI	Region of interest
SEM	Structural equation modelling
SLF	Superior longitudinal fasciculus
TBSS	Tract-based spatial statistics

1 INTRODUCTION

1.1 AGING-RELATED CHANGES IN COGNITIVE ABILITIES

Whether we are thinking of our first day in school, our shopping list, or whether we are reading a novel, imagining a scene – these activities involve cognitive processes. Cognition can be defined as "the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses" (Oxford dictionary). In this broad sense, we rely on our cognitive abilities on an everyday basis. We perceive our environment through our senses, experience what we perceive, and think about it – which increases our knowledge and understanding, deliberately or not.

Principles of human cognition have been a subject of academic interest since the ancient Greek philosophers. Within the relatively young scientific discipline of psychology, cognition has been in the focus of several lines of research. Cognitive science as an interdisciplinary field including linguistics and computer science gained momentum in the 1950s and 1960s in the USA, after a paradigm shift in psychology from the predominance of behaviorism to a predominance of cognitive psychology. Beginning much earlier, another line of psychological inquiry is concerned with mental abilities, focusing on inter-individual differences and on how to measure them. These *psychometric* approaches to cognitive abilities and intelligence have their earliest roots in the 19th century (Galton, 1869) and have been and are still used by psychologists in schools, military, and organizations, mainly with the goal to measure, compare between individuals, and predict outcomes such as educational attainment. Psychometric research did also further our knowledge about how to achieve reliable and valid measures of inter-individual differences in human mental abilities.

Human development does not end in early adulthood, but rather continues throughout the lifespan. Lifespan psychologists assume that development involves "lifelong adaptive processes of acquisition, maintenance, transformation, and attrition in psychological structures and functions" (Baltes, Staudinger, & Lindenberger, 1999). These processes can be translated to developmental goals of growth, maintenance, and the regulation of loss. In the face of age-related challenges, maintenance of resources and functions and coping with losses become focused goals and more important than gains (Ebner, Freund, & Baltes, 2006).

Although many of the fundamental ideas about lifespan development and cognitive aging have been formulated in scientific contributions since long (Tetens, 1777), the earliest standardized mental examinations of adults were conducted less than 100 years ago, documenting that the mental abilities of younger adults are, on average, greater than those of older adults (Foster & Taylor, 1920; Jones & Conrad, 1933). However, this was only the case for a certain type of mental abilities, so-called *fluid* cognitive abilities.

1.1.1 Two-component models of general intellectual ability

With regard to cognitive development, the degree of aging-related loss that is observed differs by cognitive domain, which has been recognized for a long time by scholars proposing two-component models of intellectual development (Baltes, 1987; Cattell, 1941, 1963; Horn & Cattell, 1967; Tetens, 1777). I will pick the widespread and illustrative nomenclature used by Raymond Cattell (1941, 1963) to outline differences between the two components, which he termed *crystallized* general ability and *fluid* general ability. Crystallized ability denotes the ability to perform cognitive tasks based on "skilled judgment habits", that is, habits that have been learned, and hence "crystallized". A typical example is the acquired knowledge about the world, another example is the acquired skill to perform mental arithmetic. In contrast, fluid ability is relevant "in tests requiring adaptation to new situations, where crystallized skills are of no particular advantage" (Cattell, 1963). Typical examples of fluid abilities are knowledge-independent reasoning skills, perceptual speed, working memory, and episodic memory. Fluid ability, Cattell thought, are more biologically determined, whereas crystallized ability depends more on cultural habits. Although the two factors are correlated, "they have properties differing in vital ways for education and clinical prediction" (Cattell, 1963). He predicted that the age trend for the general population in fluid ability will reach a maximum at 14-15 years, whereas crystallized ability will "increase to 18, 28, or beyond, depending on the cultural learning period for the given subculture" (Cattell, 1963).

In other words, the fluid, biologically determined abilities that enable us to solve new problems and acquire new skills and abilities, will reach an early peak, and decline during adulthood, although the crystallized, more culture-dependent, abilities, that enable us to apply tried-and-tested solutions to recognizable problems will peak later and decrease less. These predictions were in line with data on different age groups compared to one

another in early cross-sectional studies (Jones & Conrad, 1933), as well as with data on intra-individual change from later longitudinal studies (Rönnlund, Nyberg, Bäckman, & Nilsson, 2005; Schaie & Labouvie, 1974; Schaie & Strother, 1968). In a similar classification of cognitive abilities, but integrating knowledge from more fields, Paul Baltes later introduced the terms cognitive mechanics (referring to fluid) and cognitive pragmatics (referring to crystallized; Baltes, 1997, Baltes et al., 1999, Figure 1). According to this view, cognitive mechanics are indexed by "the speed, accuracy, and coordination of elementary processing operations" (Baltes, Staudinger, Lindenberger, 1999). Lifespan developmental researchers have been interested in specifying the determinants of changes in the cognitive mechanics. Aging-related changes in the cognitive mechanics (fluid abilities), can be observed for processing speed (section 1.1.4), working memory (section 1.1.5), and episodic memory (section 1.1.6), all of which are central concepts in this thesis.

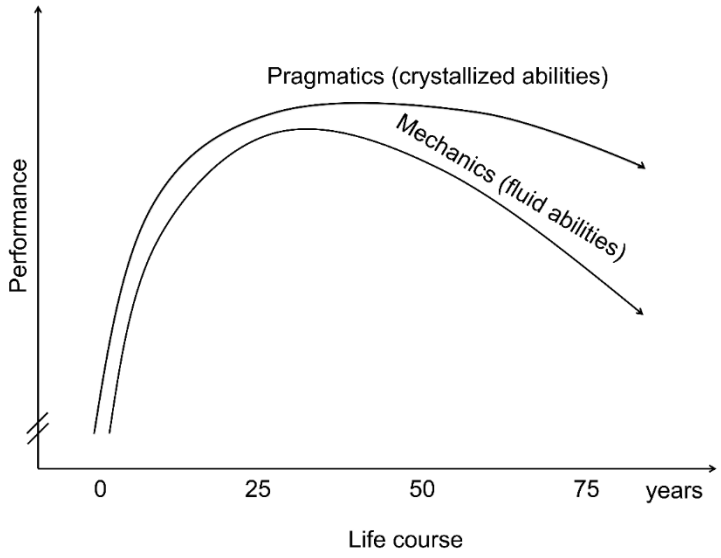

Figure 1: Cognitive pragmatics and cognitive mechanics, theoretically proposed typical developmental trajectories across the human lifespan, adapted from Baltes, Staudinger & Lindenberger (1999).

1.1.2 Differences between cross-sectional and longitudinal studies of cognitive aging

Studies of cognitive development in general or cognitive aging may use a cross-sectional design, a longitudinal design, or combinations of the two (Baltes, 1968; Schaie, 1965). In a cross-sectional study, individuals of different ages take part in a study for one occasion, and differences between age groups are interpreted as indicators of age-related differences. In a

longitudinal study, participants take part at more than one measurement occasion, and change within each individual is taken as an indication of change.

Each type of design comes with advantages and disadvantages. Cross-sectional studies are easier and more cost-effective to conduct. The main disadvantage is that the observed differences between younger and older persons are not necessarily due to chronological age, but can also be caused by differences in the time period at which the two groups were born and raised (cohort effect). A typical example of such a cohort effect would be different educational opportunities for children born at different times in history, which might result in different levels of cognitive performance. Thus, a clear advantage of longitudinal studies is that aging-related changes are measured within each cohort, thus enabling the researcher to tell apart age effects from cohort effects. This makes longitudinal designs the preferable approach in aging research (Baltes, 1968; Hofer & Sliwinski, 2001; Lindenberger, von Oertzen, Ghisletta, & Hertzog, 2011; Schaie, 1965). In theory it would be desirable to be able to follow the same individuals though their lifetimes, but as that is obviously difficult in practice, the longitudinal and cross-sectional approaches have been combined in so-called cohort-sequential designs, in which cohorts are followed over time while new cohorts are introduced (Baltes, 1968; Nilsson et al., 1997; Schaie, 1965). The main practical challenges with any longitudinal data collection are that the same participants need to be convinced to come back, and the same procedures need to be kept over time in order to make measurements comparable over time. Often-mentioned drawbacks with longitudinal data on cognitive performance are retest effects and selective attrition. Retest, or practice effect, denotes that participants tend to improve in performance by merely repeating the test procedure. A common way of minimizing the impact of retest effects is to use different versions of the same test at different measurement occasions. Selective attrition describes the situation in which persons who drop out of a longitudinal study differ from those who continue in aspects relevant to the research question. For example, individuals who develop a mobility limitation after one measurement occasion are less likely to participate in the next one, and also more likely to experience cognitive decline. In consequence, the participants of the later occasion are positively select. However, even though selective attrition leads to missing data, cross-sectional studies lack data on intra-individual change completely, which can be seen as an extreme case of missingness (Lindenberger et al., 2011; Figure

2). In consequence, longitudinal and cross-sectional data can lead to different conclusions.

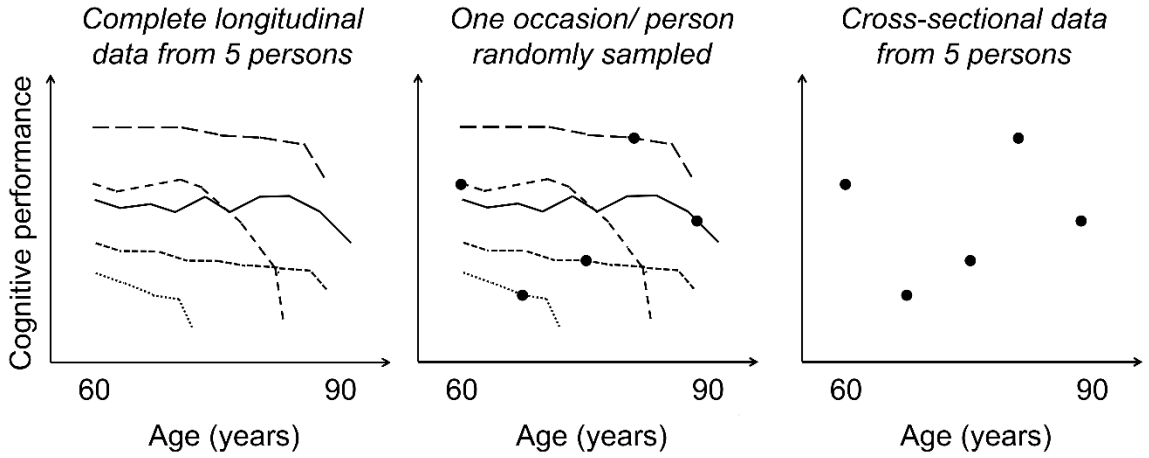

Figure 2: Cross-sectional data as a form of extreme missingness, an illustration with fictional data. On the left, complete data from 5 persons is illustrated. In a cross-sectional study, performance at one measurement occasion for each person is randomly sampled, providing a snap shot of the person's trajectory (middle). The remaining data on the trajectory of that person remains missing in the data-set of a cross-sectional study (right). Inspired by Lindenberger, von Oertzen, Ghisletta, & Hertzog (2011).

With respect to cognitive aging, longitudinal studies suggest a later onset of mean decline than do cross-sectional studies (Rönnlund et al., 2005; Schaie & Labouvie, 1974; Schaie & Strother, 1968). These differences can however partly be explained by retest effects, as could be demonstrated with data from the Betula study (Rönnlund et al., 2005).

Studies I, **II**, and **IV** in this thesis are based on longitudinal data on cognitive performance, whereas **Study III** is based on cross-sectional data.

1.1.3 Group average vs. inter-individual differences

When trying to understand cognitive aging, a very basic but meaningful general distinction to keep in mind is that between group *average* and *inter-individual differences* (or *mean* and *variance*). When, in a cross-sectional study, mean differences between age groups are observed, there is often also considerable variance around that mean. In other words, whereas the average older person may perform worse than the average younger person on a cognitive test, there will be some older persons performing at the same level as many younger persons (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012). That is, being older does not imply worse performance in a

deterministic way. Similarly, in longitudinal data, change in cognitive performance over time might imply aging-related worsening in cognitive performance for many, but not all, older adults. Some might even improve cognitively over time. From longitudinal data, a trajectory of change across occasions can be computed for each person. If the data are from older persons only, the average of these trajectories might be negative, although inter-individual differences indicate that there are persons with steeper decline as well as persons with less decline than average. These inter-individual differences in intra-individual change are of major interest in **Studies I**, **II**, and **IV**, where we try to relate them to inter-individual differences in lifestyle factors. In **Study III**, we are interested in inter-individual differences in level of performance in relation to inter-individual differences in lifestyle factors.

1.1.4 The processing-speed account of cognitive aging

One of the most robust findings in the cognitive aging literature is that older individuals are slower in responding to a task than younger persons, and that individuals tend to get slower in responding as they age. Processing speed accounts of cognitive aging propose that differences between younger and older individuals in how well they perform on many cognitive tasks can, to a large extent, be accounted for by the older persons being relatively slower in cognitive processing (Lindenberger, Mayr, & Kliegl, 1993; Salthouse, 1996). Salthouse (1996) proposed two mechanisms as responsible for the association between processing speed and cognition. The *limited time mechanism* is thought to be at work in a situation in which a cognitive operation needed to complete a task cannot be completed in time, because execution is too slow. That is, if the task consists of a sequence of operations, later operations cannot be completed with the given time limits. A necessary assumption here is that there are external or internal time limits for the execution of the operation. The *simultaneity mechanism* is thought to be at work when several pieces of information need to be available at the same time. Slow processing hinders the synchronization of the constituent tasks, meaning that a piece of information available first is already lost when the next piece has been made available. A necessary assumption is that information can be "held available" only for a certain amount of time (Salthouse, 1996). Whether one or the other mechanism is at work might depend on the nature of the task at hand and the cognitive processes involved in solving it.

Empirical evidence in support of the processing speed account is derived from cross-sectional (Salthouse, 1996, Lindenberger et al., 1993) and longitudinal (Finkel, Reynolds, McArdle, & Pedersen, 2007; Ghisletta & Lindenberger, 2003) studies. Importantly, longitudinal studies show that within-person changes in processing speed precede and predict changes in knowledge (Ghisletta et al., 2003), memory, and spatial abilities (Finkel et al., 2007).

Different types of tests have been used to measure processing speed, varying by research tradition, and measuring different components of processing speed. In **Studies I**, **II**, and **IV**, we use measures of *perceptual speed* as a proxy for processing speed. As often done in similar studies, we assessed perceptual speed by speed of responding on a paper-and-pencil tests with the content being so simple that everyone would be able to complete without errors if there were no time limits. "Perceptual speed tasks often involve elementary comparison, search, and substitution operations, with the test score consisting of the number of items correctly completed in the specified time" (Salthouse, 2000). However, measures of perceptual speed vary in purity, that is the degree to which they also require so-called higher-order cognitive functions such as goal maintenance, manipulation of information in working memory, and decision-making (Cepeda, Blackwell, & Munakata, 2013).

1.1.5 Aging-related changes in working memory

Another domain of fluid cognitive ability that is affected by aging is *working memory* (Verhaeghen & Salthouse, 1997). Working memory involves the simultaneous storage and processing of information (Baddeley, 1992; Baddeley & Hitch, 1974). Baddeley and Hitch (1974) viewed working memory as "a brain system that provides temporary storage and manipulation of the information necessary for such complex cognitive tasks as language comprehension, learning, and reasoning." This model assumes more than one storage system and a central controlling unit. The control unit is termed "central executive" and coordinates the information stored in two "slave systems", the "phonological loop" and the "visuospatial sketchpad". The former is thought to temporarily store and manipulate speech-based information, and the latter is thought to store and manipulate visuospatial information (Baddeley, 1992; Baddeley & Hitch, 1974).

The concept of working memory has proven fruitful both in cognitive science and neuroscience and in the research on inter-individual differences and the factor structure of intelligence. Experimental studies in

the fields of cognitive psychology and neuroscience have since advanced knowledge about the constituent components of working memory, further specifying the processes involved. Psychometric studies have suggested that inter-individual differences in working memory are closely related to differences in fluid abilities in general (Engle, Tuholski, Laughlin, & Conway, 1999). Key findings are that there are inter-individual differences in working memory capacity (Kane & Engle, 2002), and that these differences are predictive of differences in fluid abilities such as abstract reasoning, mathematics, language, and overall academic performance (Cowan et al., 2005; Daneman & Carpenter, 1980; Unsworth, Fukuda, Awh, & Vogel, 2014). Inter-individual differences in working memory performance are largely determined by inter-individual differences in attentional control rather than the absolute amount of storage space (Adam, Mance, Fukuda, & Vogel, 2015). Further, working memory performance normally increases during childhood and adolescence (Gathercole, Pickering, Ambridge, & Wearing, 2004), deteriorates in old age (Nyberg, Dahlin, Stigsdotter Neely, & Bäckman, 2009; Rieckmann, Pudas, & Nyberg, 2017), and is sensitive to training (Karbach & Verhaeghen, 2014).

A recent model of working memory differentiates the central processes of maintenance and manipulation and specifies their sub-processes and links these to activation of relevant brain areas and networks (Eriksson, Vogel, Lansner, Bergstrom, & Nyberg, 2015). Eriksson and colleagues (2015) conceptualize working memory as "a particular state of a representation (temporarily enhanced accessibility), regardless of the kind of representation". Specifically, attentional processes and prospection are involved in solving a working memory task and in the mental representations of the memorized items stored in perceptual and long-term memory (Eriksson et al., 2015). Which brain regions are involved depends on the type of information to be maintained, or accessible. Maintenance of visually represented information draws on temporal regions, whereas maintenance of spatial information involves parietal areas. These patterns have been shown in patients with brain lesions, and in imaging studies on healthy participants (Eriksson et al., 2015; Postle, 2015). Executive aspects of working memory activate the prefrontal cortex together with the parietal cortex, with the latter mainly implementing selective attention, and the former maintaining representations of the task set goals. The striatum has been suggested as a gatekeeper that regulates whether representations in the prefrontal cortex should be maintained or updated (Eriksson et al., 2015; O'Reilly & Frank, 2006). More brain regions are involved in some of the

sub-processes, and in orchestrating the activity of these different regions, large-scale brain networks are taxed (Eriksson et al., 2015).

An example of a widely used type of working memory task is the n-back task, in which participants are presented with a sequence of items (e.g. words, letters, numbers, shapes), one at a time and are requested to press a button as soon as the current item is identical with an item n times back in the sequence. The higher the n, the higher the working memory load, and the more difficult is the task. A version of an n-back task is used in **Study III.**

1.1.6 Aging-related changes in episodic memory

Memory is a cognitive function that requires a complex set of cognitive processes, and can be subdivided into different components. Among the most influential subdivisions in memory research is the division into the three subsystems procedural, semantic, and episodic memory (Squire & Zola-Morgan, 1991; Tulving & Donaldson, 1972; Wheeler, Stuss, & Tulving, 1997). Procedural memory refers to memory of how to perform a task (such as how to ride the bike). It is based on learning or experience that does not need awareness, and hence often termed implicit or non-declarative. By contrast, semantic and episodic memory are both explicit or declarative forms of memory (Figure 3). Semantic memory denotes knowledge about the world (such as what a bike looks like), and episodic memory refers to the type of memory that allows us to consciously recollect our own experiences as they are located in time and space (e.g. how we saw that elk on a bike trip last summer). Episodic memory relies on a sequence of the processes of encoding, consolidation, and retrieval of information (Squire, 1992; Wheeler et al., 1997). Episodic memory performance shows larger age-related declines than semantic or implicit types of memory, and is one of the earliest signs of impending dementia (Bäckman, Jones, Berger, Laukka, & Small, 2005; Rönnlund et al., 2005). These varieties of memory are linked to fluid ability (episodic memory) and crystallized ability (implicit and semantic memory), respectively (section 1.1.1).

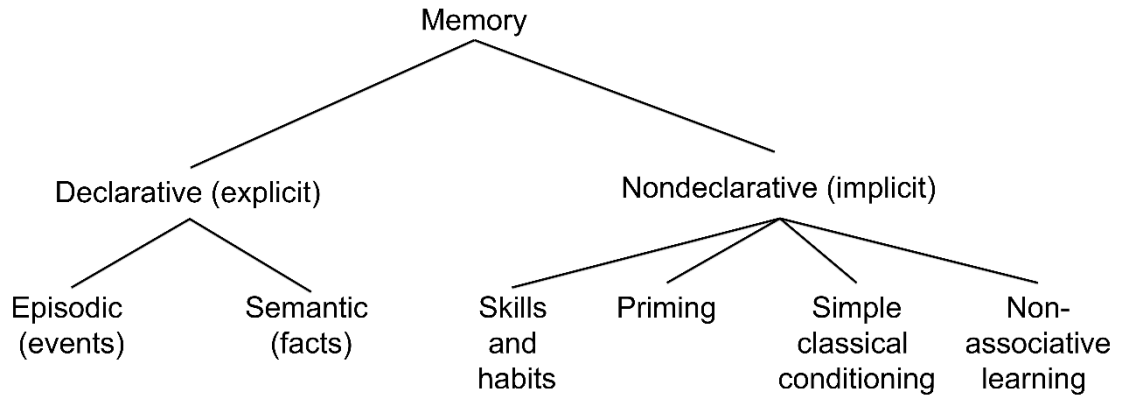

Figure 3: A classification of memory. Declarative memory denotes the conscious recollection of facts and events. Non-declarative memory refers to types of memory that non-consciously result in behavioural changes. Adapted from Squire & Zola-Morgan (1991).

Tasks to probe episodic memory typically involve a study phase in which participants are presented with the material to-be-remembered (encoding phase), a delay period, and a test phase in which the participants are asked to recollect the information (retrieval phase). Different types of tasks require different ways of retrieving information from memory. In free recall tasks, participants are asked to freely recall as many items as possible from the studied material. In recognition tasks, they are presented with items and asked to indicate whether or not they have encountered the item in the study phase. Recognition of a given item can be based on conscious recollection or a feeling of familiarity, and while recollection tends to be more difficult for older than for younger persons, the sense of familiarity seems relatively unaffected by age (Koen & Yonelinas, 2016). In **Studies I** and **III**, we use measures of episodic memory.

1.1.7 Analysing inter-individual differences with structural equation modelling

In the studies of this thesis, my co-authors and I are interested in between-person variance in cognition and the variance-covariance structures of performance in cognitive tests and other variables. We use methods from the psychometric tradition of investigating human cognition. In other words, we are looking at questions such as, if a person is good at solving task A, compared to other persons in the sample, does the person tend to be relatively good at task B, too? If that is not the case across persons, the tasks do not seem to measure the same ability of a person, the basic logic goes. The ability level of a person is then estimated on the basis of several tasks

that are thought to require this ability, using a statistical method called factor analysis. All associations we report reflect associations between inter-individual differences in one variable and inter-individual differences in another variable. A positive association between two variables means that a person with a high value in one variable (high compared to the other persons) will likely have a high value in the other variable as well. A negative association means that a person with a high value in one variable will have a low value in the other variable. Inter-individual differences are also called *variance*, and associations between variables are called *coviariance* or *correlation* (the standardized covariance). In analyses with many variables, many variances and covariances are observed. *Confirmatory factor analysis* (CFA) is a statistical method to analyse such variance-covariance structures. It can be used to extract variance that is common in performance measures across different tasks. This common variance across tasks is interpreted as a "latent", not directly observable, ability, that is a common cause to performance differences across all tasks. All "residual" variance, that is, variance unique to performance in a specific task, is estimated separately. Conceptually, this residual variance is a combination of task-specific and measurement error variance. Modelling inter-individual differences in cognition as latent variables using CFA comes with the advantage that measurement error is separated from the estimation of the between-person differences in the cognitive ability of interest. In all studies of this thesis, we use CFA to model cognitive performance.

We combine many CFA's using structural equation modelling (SEM; Jöreskog & Sörbom, 1989; Kline, 1998). SEM is a general and flexible approach to analyze covariance structures. A structural equation model can consist of any possible combination of CFA and path analysis. In path analysis, several regression equations are combined and estimated at the same time, with the possibility of any variable to be a predictor and an outcome at the same time. In SEM, several associations in the form of regressions or covariances among latent and observed variables can be estimated simultaneously (Figure 4). The general principle behind SEM is that the user specifies a statistical model which is fitted to the data using an approximation algorithm, in the case of parametric data, mostly using a maximum likelihood estimation. This approach aims at finding the estimates for the set of parameters in the statistical model, such as the covariance between two latent variables, that maximize the likelihood of the data to be drawn from a population in which these parameters were true. can be fixed to a certain value. When setting up a model, parameters can be fixed to a

certain value (such as setting a covariance to zero, if the variables are assumed to be orthogonal in the model). All parameters that are not fixed will be estimated in an optimization process, finding the set of parameters that best represents the data. It is important to keep in mind that different models can describe the data similarly well; when a specific model fits the data well, this does not preclude other models to also fit the data well. In general, no SEM is true or false, it just describes variance-covariance structures in a parsimonious, thus simplifying, way. The SEM should represent a theoretical model, thus a certain simplification of the truth, and can be used to check whether the observed data is compatible with the theoretical model at hand.

When applied to developmental questions, SEM can be used to formulate and test aging-related change in the loading structure of a CFA, in variances and covariances of latent factors, and means of latent factors (Baltes & Labouvie, 1973). In the models specified in the present thesis, we assume the loading structures not to change over time. Our focus lies on means, variances and covariances. The main advantages of using SEM in the here are as follows: When applied to the cognitive performance data, the measurement models (CFA's) in our SEMs allowed us to separate task-specific variance from task-independent variance as a purer measure of inter-individual differences in a given cognitive ability. Similarly, when we defined measurement models to brain data, we extracted variance common to the two hemispheres to obtain a purer measure of inter-individual differences in a given structure. As latent variables are theoretically free of measurement error, associations among them are more easily detected than associations between observed variables (von Oertzen, Hertzog, Lindenberger, & Ghisletta, 2010).

In **Studies I**, **II**, and **IV,** we specified a longitudinal SEM termed latent change model (LCM; McArdle and Nesselroade, 1994), which includes estimating a latent change score that indicates the difference between the latent variable at two time points (Figure 4). In multivariate LCM, we combined several LCM and estimated covariances among the latent change scores. In so doing, we took advantage of the change scores being theoretically error-free to increase the statistical power to detect change-change associations (von Oertzen et al., 2010). A further advantage of using SEM with longitudinal data is that it allows for a good handling of missing data. When SEMs are fitted to the data using a full-information likelihood estimation, all information in the data is used to estimate the

model parameters, even if data are only partly available (e.g. data only for the first time point in an individual who dropped out of the study).

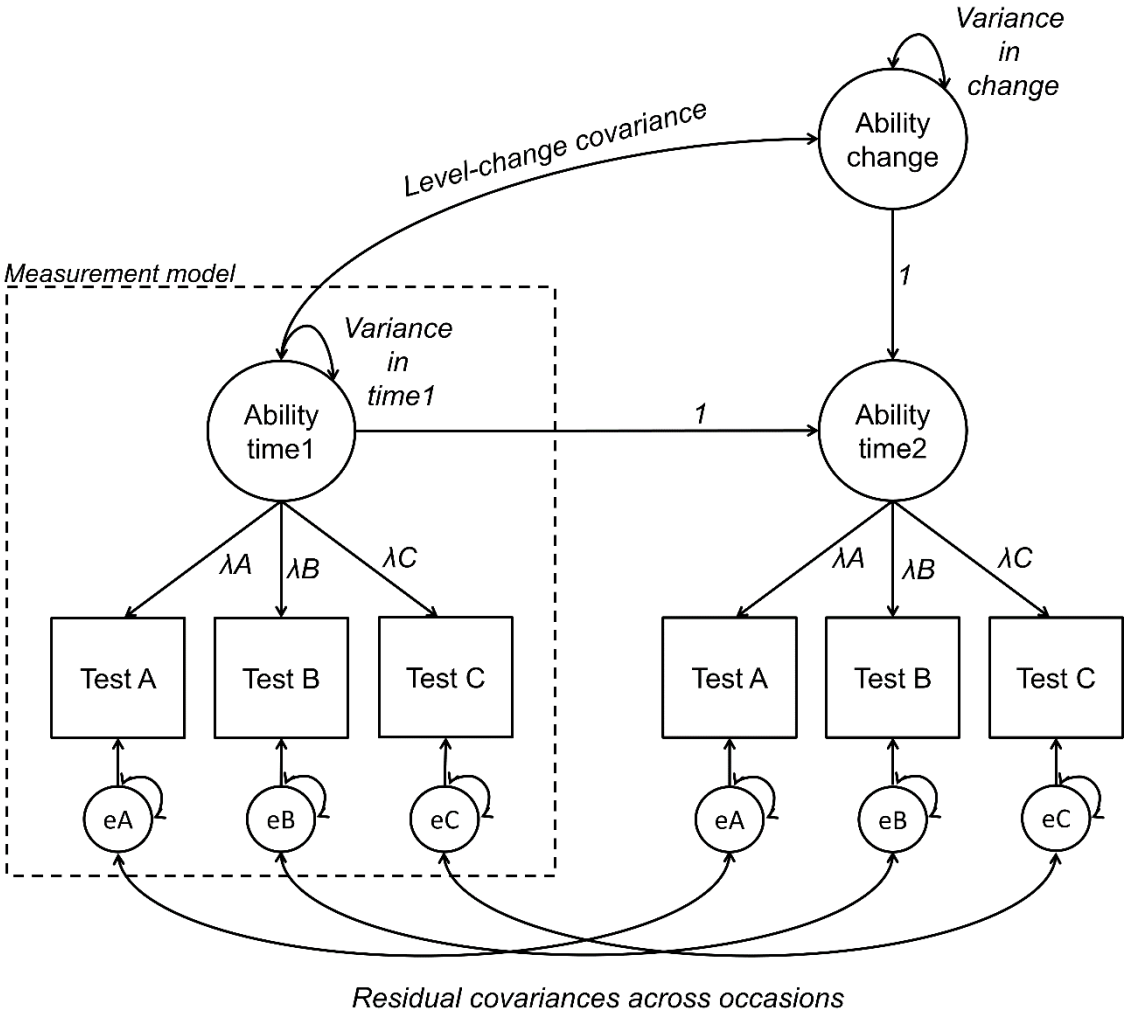

Figure 4: Example of a latent change score model (LCM). The measurement model (example in dashed frame) is a confirmatory factor model with a latent ability variable (circle) and three observed test scores (squares). One-headed errors represent regression paths, and double-headed errors represent variances and covariances. The latent ability "loads" on the test scores, with a loading parameter estimated separately for each test score (λA, λB, λC), which indicates the degree to which variance in the test score is related to the latent score. All variance in a test score that is not related to the latent score is represented in a residual variance term (eA, eB, eC). The same measurement model is defined to model the ability at a second measurement occasion (Ability time2). A latent change score (Ability change) is added, and by fixing the weight of the regression of Ability time2 on Ability time1 to 1 and simultaneously fixing the regression weight of the regression of the change score on Ability time 1 to 1, the change score is defined to represent the Ability time2 – Ability time1 difference. In addition to the variance in Ability time1 and in the change score, the covariance between the two is estimated. (Means are not depicted in the figure, but we estimate the means of Ability time1 and Ability change, and the indicator intercepts, except for the first one, which is fixed for scaling purposes).

As any other model, also a mediation model can be fitted to the data. A mediation model assumes that part of or all variance shared between two variables is also shared by a third variable, which would suggest that the third variable is possibly causing the association between the other two variables (Shrout & Bolger, 2002). Note that as with other SEM, mediation models cannot test whether such a causal assumption is true. Rather, "all it does is tell us how the world may look if that [causal] assumption were true" (Lindenberger & Pötter, 1998). We performed a mediation analysis in **Study II**.

1.2 BRAIN CHARACTERISTICS ASSOCIATED WITH COGNITIVE AGING

Hosting the biological substrates of cognitive functions, the brain expectedly changes with aging as well. Age-related differences in the brain can be observed on many levels such as macrostructure (Raz & Lindenberger, 2013), microstructure (Bender, 2014; Bender & Raz, 2015), neuronal activation, and neurotransmitter levels (Bäckman et al., 2011; Bäckman, Lindenberger, Li, & Nyberg, 2010; Nyberg et al., 2016). As with cognition, there are marked inter-individual differences in level and rate of change for most indicators of brain integrity in late life. As the technological devices needed to study the brain's structure and functions are costly and subject to frequent technological innovations, fewer large-scale longitudinal studies have been performed on brain aging than on cognitive aging. **Studies I** and **II** investigate changes in white matter microstructure in very old age (above age 80) in relation to changes in perceptual speed. **Study III** examines levels of dopamine D2 receptor availability in an age-homogeneous sample of individuals in their mid-sixties and their relation to perceptual speed, working memory, and episodic memory performance.

1.2.1 Aging-related changes in white matter microstructure

White matter in the brain consists of axons, the "arms" of neurons, attached to the soma of a neuron reaching out to other neurons to connect with them via synapses. In large white matter tracts, axons are bundled to thick white matter fiber bundles that connect different regions of gray matter in the cortex, in subcortical nuclei, and with the spine and the rest of the peripheral nervous system, but white matter also exists interspersed with grey matter in cortex and subcortical nuclei. Each axon that is part of white matter is wrapped in a sheath of myelin, a fatty white substance grown from glial

cells, that electrically insulates the axon. Myelin is the substance that makes white matter appear white in dissected brains and was first discovered by Rudolf Virchow in 1854. The electrical signal that is propagated along an axon in form of an action potential is propagated much faster when the axon is myelinated. The myelin sheaths are interrupted by small unmyelinated ("naked") rings around the axon (*nodes of Ranvier*) with abundant sodium channels, causing the action potential to "jump" from one node of Ranvier to the next instead of travelling continuously along the depolarizing axon (Figure 6). Demyelination occurs in several diseases such as multiple sclerosis and results in diverse symptoms depending on where in the brain or the peripheral nerve system it occurs.

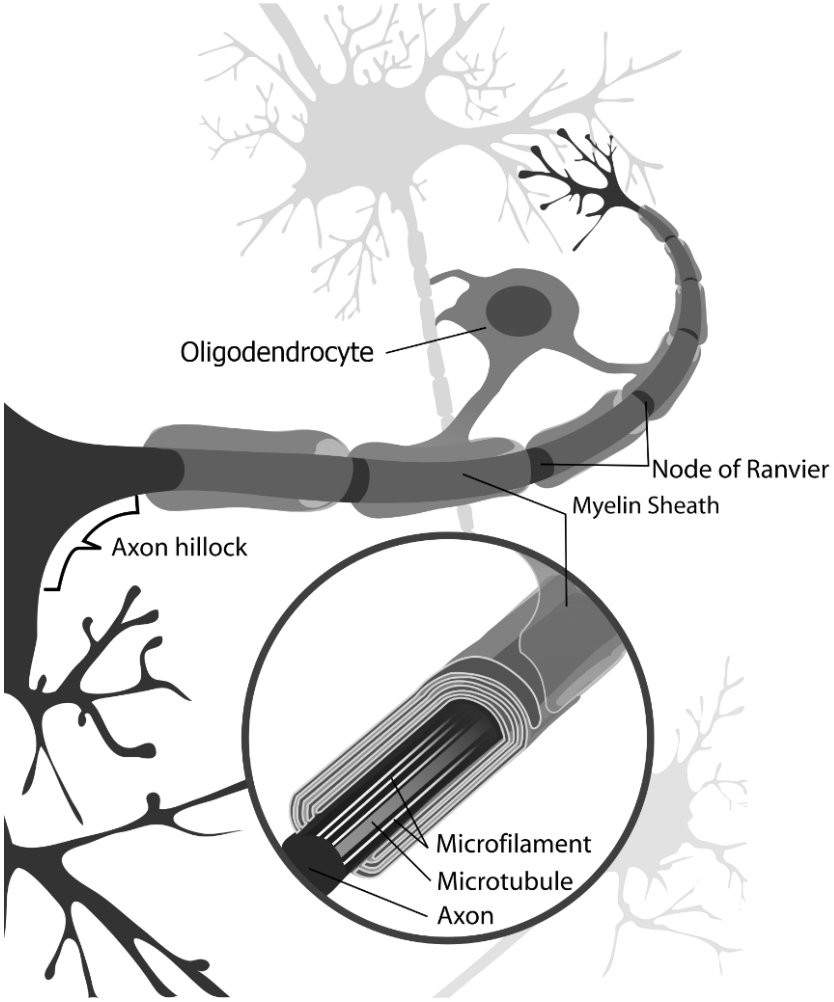

Figure 6: Illustration of an axon wrapped in myelin sheaths. The axon is linked to the neuron's soma at the "axon hillock". An oligodendrocyte, a type of glial cell, builds outgrowths that form the myelin sheaths. In the cross-section of the axon, microfilaments and microtubules, small structures within the axon are visible (© Andrew C, Wikimedia commons)

The microstructure of the brain's white matter can be assessed with diffusion tensor imaging (DTI) in humans. DTI measures reflect the directionality of white matter microstructure, which is partly determined by the cell membrane and the intracellular structure along the axons and to a large extent by the myelin sheaths around them. Therefore, white matter

microstructure is closely linked to the speed with which information is transmitted within and between large-scale neural systems (Andrews-Hanna et al., 2007; Catani & Ffytche, 2005; Fields, 2008; Geschwind, 1965). DTI is an MRI technique that makes use of strong magnetic fields and field gradients to measure the diffusion of water molecules in tissue. For each voxel in the brain, several parameters can be derived, such as the rate and direction of diffusion, using DTI. In intact white matter tracts, the main direction of diffusion is along the path of the tract, since water molecules will largely travel along the axons and rarely cross the cell membranes, and they cannot cross myelin. Fractional anisotropy (FA) is a DTI parameter that indicates the preferred direction of diffusion and high FA reflects high fiber density and coherence within a voxel, which is typically interpreted as indicating relatively intact white matter. Mean diffusivity (MD) measures the rate of diffusion in all directions, and high MD indicates less dense microstructure (Field, 2008).

White matter microstructure as measured with DTI in humans shows pronounced cross-sectional age differences (Burzynska et al., 2010; Sullivan & Pfefferbaum, 2006) as well as decline with aging (Barrick, Charlton, Clark, & Markus, 2010; Bender & Raz, 2015; Charlton, Schiavone, Barrick, Morris, & Markus, 2010). White matter microstructure is related to cognitive performance (Bender, Prindle, Brandmaier, & Raz, 2016; Madden, Bennett, & Song, 2009; Persson et al., 2006) and improves with cognitive training in both younger and older adults (Lövdén, Bodammer, et al., 2010). Charlton et al. (2010) observed significant 2-year whole-brain decreases of FA and increases of MD in a sample of adults aged 50–90 years (see also Barrick et al., 2010). Changes in indices of whole brain MD were significantly related to changes in working memory performance, but not to changes in perceptual speed and executive functioning. Studies published before **Study I** of this thesis thus suggested change-change associations between white matter microstructure and cognitive performance in aging, but were restricted to global measures of white matter microstructure (across the whole brain). However, previous studies had suggested functional specificity of several white matter tracts (Catani & Ffytche, 2005), and a considerable amount of tract-specific variance in inter-individual differences in FA and MD. We therefore chose to examine change-change associations between white matter microstructure (FA and MD) and cognitive performance tract by tract. We chose this approach in **Studies I** and **II**.

1.2.2 Aging-related changes in dopamine

DA is an organic chemical of the family of catecholamines and acts as a neurotransmitter in the brain. For its discovery as such in the 1950s, Arvid Carlsson was awarded the Nobel prize in medicine and physiology in 2000. DA is crucially involved in motor functions, learning and memory, and in reward-motivated behavior. Many addictive drugs increase DA-dependent neural activity. Dysfunction of DA-ergic neurotransmission is implicated in a range of neurodegenerative and neuropsychiatric disorders (Schultz, 2007).

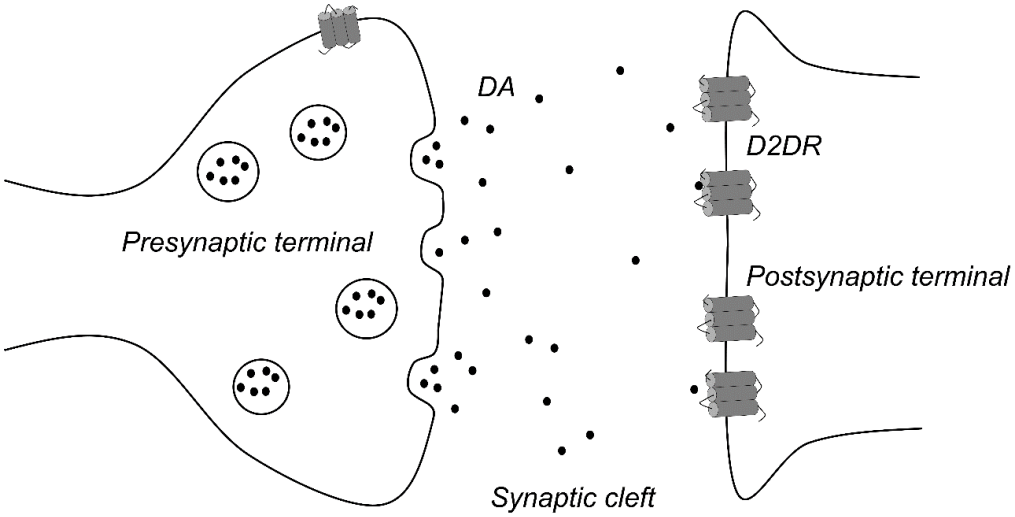

Figure 6: Illustration of dopaminergic signal transmission at a synapse in striatum with D2 receptors. In the presynaptic terminal, which is part of a neuron's axon, DA has been synthesized and packaged into vesicles. When the presynaptic neuron is firing, an action potential will eventually arrive at the presynaptic terminal and triggers the vesicles to merge with the cell membrane, releasing the dopamine (DA) into the synaptic cleft. Some of the DA molecules will eventually bind to one of the D2 receptors in the membrane of the postsynaptic terminal of the receiving neuron, causing reactions specific to the type of neuron.

DA is most abundant in striatum, a subcortical structure in the basal ganglia. The name striatum stems from its appearance with stripes of white matter interspersed with grey matter. DA is an important neuromodulator in mainly two pathways in which striatum receives glutamatergic input from limbic, associative, and motor cortical areas, which is relayed back to cortex via basal ganglia and thalamus (Joel & Weiner, 1994). Of the two pathways, the direct pathway does not include thalamus, and DA-ergic transmission relies on D1-like receptors (D1, D5). The indirect pathway includes the thalamus and relies on D2-like receptors (D2, D3, D4). The two pathways have opposite but complementary functions, and a disturbance of the balance between the two is a major cause of movement disorders (Gerfen, 2010).

At a synapse, DA is released from the activated presynaptic neuron into the synaptic cleft and eventually binds to D1-like or D2-like receptors at the terminal of the postsynaptic membrane, depending on whether released in a firing burst (phasic) or in tonic firing pattern. Tonic release stimulates D1-like receptors (direct path to cortex), whereas phasic release stimulates D2-like receptors (indirect path via thalamus). DA receptors can be quantified with positron emission tomography (PET), an imaging technique that measures radioactivity of a radioactively labelled chemical compound, a so-called radiotracer or ligand, that is injected into a participant's blood stream and binds to a target site in the tissue before the imaging session. For the purpose of the study involved in this thesis, a ligand was chosen that specifically binds to $D_{2/3}$ dopamine receptors ($D_{2/3}$DR's), thus aiming at assessing $D_{2/3}$DR availability in the brain ([^{11}C]raclopride), focusing on striatum and hippocampus. As the radioactive ligand decays, the radiation is detected by the PET camera and registered across time and voxels in brain tissue. From time-activity curves in each voxel, a measure of binding potential (BP) is computed, which is an estimate of the ratio of specific to non-specific binding of the ligand to the target receptors, and is interpreted as an indicator of $D_{2/3}$DR availability and used in **Study III**.

DA is involved in higher-order cognitive functions, such as episodic memory (Bäckman et al., 2011; Bäckman et al., 2010; Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006; Cervenka, Backman, Cselenyi, Halldin, & Farde, 2008; Lisman, Grace, & Düzel, 2011; Nyberg et al., 2016; Shohamy & Adcock, 2010) and working memory (Cools & D'Esposito, 2011; Liggins, 2009; Takahashi, 2013; Takahashi et al., 2008). Probed with various markers in cross-sectional studies, DA functioning has been shown to deteriorate with aging, forming a correlative triad among aging, DA, and cognition (Bäckman et al., 2011; Bäckman et al., 2010; Rieckmann, Karlsson, Fischer, & Backman, 2011).

1.2.3 Theoretical frameworks on inter-individual differences in cognitive and brain aging

Why do persons differ from one another in level of cognitive performance and in rate of aging-related changes? Inter-individual differences in cognitive ability emerge during early childhood and persist or increase over the lifespan, determined by an interplay of genetic predispositions, epigenetic changes, and environmental differences and their complex interplay (Freund et al., 2013; Molenaar, Boomsma, & Dolan, 1993). In contrast to cognitive development in early life, there is no strong genetic

program that determines cognitive development in late life (Kirkwood, 2005; Lindenberger, 2014). Evolutionary theories of aging suggest that rather than being genetically programmed, biological aging occurs as a result of accumulating damage, which itself results from evolved limitations in the maintenance of physical functions (Kirkwood, 2005). Accumulating damage in the brain is plausibly suspected to be responsible for cognitive aging but exactly in what ways is not yet fully understood. Although successfully done in more and more studies, mapping declining cognitive performance to neurochemical, structural, and functional brain changes is not trivial. Theoretical approaches that relate inter-individual differences in cognitive aging and their relation to brain aging are cognitive reserve, brain reserve, brain maintenance, scaffolding/ compensation, and brain plasticity. These approaches are not mutually exclusive, do partly overlap and partly complement each other. Note that the theoretical approaches on cognitive and brain aging that are shortly portrayed here shall serve as a background for this thesis but are not meant to be directly tested here.

1.2.3.1 Cognitive reserve and brain reserve

Cognitive reserve denotes how "inter-individual differences in how people process tasks allow some to cope better than others with brain pathology" (Stern, 2002, 2009), and has been proposed to explain the observation that the degree of brain pathology in a person does often not directly correspond to the clinical manifestation of cognitive impairment. In other words, a person can present with considerable brain pathology that suggests symptoms of dementia, yet the person does not show any such symptoms. The notion of cognitive reserve has been used to explain epidemiological findings that associate educational and occupational exposure and leisure activities with reduced risk of dementia and slower rate of cognitive decline in healthy aging. In a refinement of his concept of cognitive reserve, Stern (2009) suggested two possible neurobiological mechanisms in which cognitive reserve might be at play. One of them is the efficiency, capacity, or flexibility of brain networks. More efficient, capable, or flexible brain networks might allow for proficient cognitive functioning even in the face of brain pathology. The other biological mechanism is compensation, implemented by using other brain structures or networks if the structures or networks normally used for a given task are disrupted by pathology.

A related concept is brain reserve (Stern, 2009), which has been used to describe inter-individual differences in the brain's ability to cope with pathology. Inherent to this notion is that brain reserve capacity is

limited, implying that, when capacity is reduced, a threshold will be hit and functional deficits will emerge. Indicators of brain reserve can be brain size or number of neurons. Brain reserve has also been described as passive reserve, because it is assumed to be rather stable within individuals, and because the effects will be the same for everyone after the threshold is hit. In contrast, cognitive reserve can be viewed as active, because it is thought to be malleable within individuals (Stern, 2009).

1.2.3.2 Scaffolding

The scaffolding theory of aging and cognition (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014) was formulated to conceptually integrate findings from functional and structural neuroimaging studies of aging and builds on the idea that inter-individual differences in cognitive performance are determined by the balance between inter-individual differences in age-related structural and functional deterioration in the brain and differences in the degree of compensatory activity in the brain, termed "compensatory scaffolding". Findings of greater activation or additional recruitment of brain areas by older compared to younger adults (Gutchess et al., 2005), as well as strengthened connectivity and neurogenesis can be thus interpreted as scaffolding processes in this approach (Reuter-Lorenz & Park, 2014). Experience-dependent changes in the brain, e.g. after new learning, cognitive training, or engagement in intellectual activities, are thought to affect these compensatory scaffolding processes and are thought to result in both higher levels and slower decline in cognitive performance (Reuter-Lorenz & Park, 2014).

1.2.3.3 Brain maintenance

The fact that some individuals reach old age without apparent cognitive decline can also be simply due to their relatively intact brains. In a note on "brain maintenance", Nyberg and colleagues (2012) remind the readers of the theoretical possibility of a match between maintained brain capacity and preserved cognitive functioning. Brain maintenance thus denotes the relative lack of pathology in the aging brain. Empirically, this is evident in inter-individual differences in the amount of neurochemical, structural, and functional brain changes in late life, and in positive associations between changes in brain properties and cognitive performance. Studies investigating and documenting such change-change associations are still rare (Bender et

al., 2016; Persson et al., 2012; Pudas et al., 2013; Rieckmann et al., 2017; S. J. Ritchie et al., 2015), and we contribute to the evidence in **Study I.**

1.2.3.4 Plasticity

Plasticity can be defined as the organism's capacity for reactive change in anatomical structure, driven by "a prolonged mismatch between functional organismic supplies and environmental demands" (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010). These plastic changes enable the organism to change the range of "behavioral flexibility", or the behavioral repertoire, e.g. the individual range of cognitive performance. The human brain adaptively changes its structure in response to environmental demands, or experience, even in late life, as has been demonstrated in several cognitive training studies (Brehmer, Kalpouzos, Wenger, & Lövdén, 2014; Lindenberger, Wenger, & Lövdén, 2017; Lövdén, Wenger, Mårtensson, Lindenberger, & Bäckman, 2013; Raz et al., 2013; Zatorre, Fields, & Johansen-Berg, 2012). Brain plasticity is thus one possible mechanism by which individual differences in cognitive aging emerge. As individuals are faced with different environmental demands, their brains may adapt to the demands posed.

1.3 LIFESTYLE AND COGNITIVE AGING

Within a range of possible late-life cognitive trajectories that are theoretically possible for a person with a given level of physical functioning and given social and cultural opportunities, personal lifestyle choices can have an impact on the person's trajectory of change. Even small improvements or postponements of decline in cognitive performance can potentially postpone the age at which the person is hitting a threshold of functional impairments such as developing dementia.

One of the factors that has received much interest in the public discourse as well as in research is engagement in activities (Hertzog, 2009). Among all lifestyle choices that potentially affect cognitive aging, leisure activities are of major interest, because they are a central part of life for most persons after retirement age (Nimrod & Janke, 2012), they are a potential source of stimulation, and possibly amenable to intervention (M. Kivipelto, Mangialasche, & Ngandu, 2017; Lövdén, Bäckman, et al., 2010; Ngandu et al., 2015; Park et al., 2014).

1.3.1 Theoretical approaches to leisure

Leisure can be defined as time free of work or other duties, but definitions of leisure encompass often more than that (Stebbins, 2012). In a qualitative interview study, adult participants associated leisure with freedom of choice, lack of constraint, ability to express oneself and to do things voluntarily (Roberts, 1999). Researchers from various disciplines, such as history, sociology, psychology, and medicine are interested in investigating leisure, and there are many ways of defining the part of the leisure concept that goes beyond mere time. One approach within sociological leisure theory is to characterize and classify leisure activities by their "meaning" for the participants (Watkins, 2010; J. Wilson, 1980). These meanings influence motivation and experience. In contrast to leisure behaviour, age-related changes in subjective leisure meaning and experience have been rarely researched (Gibson, 2006). In our approach to activities in **Studies II, III**, and **IV,** we take aspects of experience into account. In **Studies II** and **IV,** we assess aspects of experience from a rating sample of similar age and background as the study sample. In **Study III**, we collect subjective ratings of experienced physical demands from the participants.

1.3.2 Assessing leisure activity engagement

Although leisure activity engagement has been extensively studied since decades, no standard way of operationalizing and measuring has been developed (Bielak, 2010; Kleiber & Genoe, 2012). Attempts to establish a general taxonomy are complicated by the fact that the meaning of many activities differs between cohorts and cultural backgrounds (Bielak, 2010; Kleiber & Genoe, 2012; Lawton, 1993). In observational studies, participants are most commonly asked to self-report how frequently they normally engage in activities listed on a questionnaire. Sometimes more direct measures such as experience sampling and/or accelerometers or other mobile activity monitors are used. When questionnaires are used, they mostly assess the number of activities engaged in and the frequency of engagement. How many and which activities are listed on the questionnaires varies greatly across studies (Fallahpour, Borell, Luborsky, & Nygard, 2016; Yates, Ziser, Spector, & Orrell, 2016), which is a logical consequence of the fact that the typical activity patterns are different in different countries and cultures within countries.

To reduce data complexity and to grasp different aspects of leisure activity engagement, researchers often classify activities according to

different objective or subjective characteristics. This classification differs across studies; many authors choose to classify activities as either physical, mental (also called cognitive, intellectual), or social (Bielak, 2010; Fallahpour et al., 2016; Hertzog, Kramer, Wilson, & Lindenberger, 2009; Yates et al., 2016). This categorization approach leads to two major conceptual difficulties. First, it ignores the multidimensional nature of activities (Karp et al., 2006; Yates et al., 2016). For instance, dancing can be characterized as both physical and social, whereas watching TV has very little of each component (Figure 7). By classifying each activity according to its most salient feature, one risks losing information about its other features. Second, parts of the activity characteristics depend on subjective experience and might therefore differ between individuals. More specifically, the physical, mental and social aspect of a given activity might depend on personal capacities (e.g. the physical and mental aspect of travelling for an average person of 85 vs. a person of 60 years) and life circumstances (e.g. the social aspect of going to the cinema for a person going alone vs. a person accompanied by a spouse, relative, or friend). As both capacities and circumstances tend to change with aging, common sense judgments about activity characteristics might not match the experience of elderly study subjects. Thus, assessing some information about how participants experience a given activity along with information about how often the person engages in the activity would be desirable (and is done in **Study III**). If that is not possible, one alternative is to assess expert ratings about the activities and use these to characterize leisure activity engagement in multidimensional space (Karp et al., 2006; J. R. B. Ritchie, 1975).

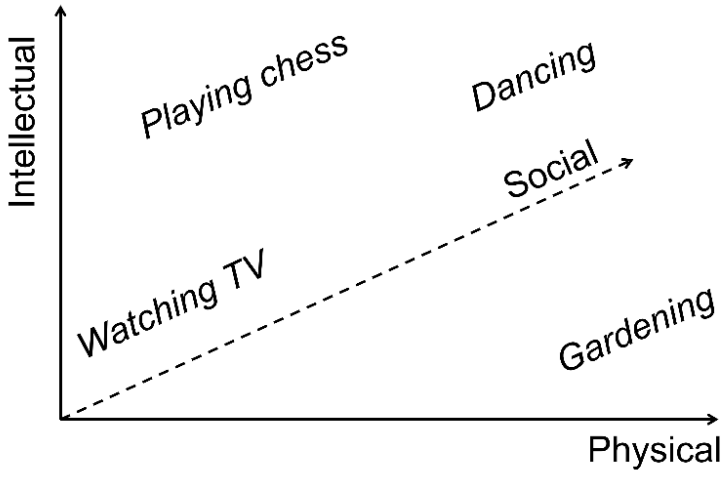

Figure 7: Illustration of the multidimensional nature of leisure activities. Watching TV scores low on all components, dancing scores high on all components, playing chess scores high on intellectual component, and gardening scores high on physical component.

This latter approach is used in **Studies II** and **IV**. With this we aimed to find activity clusters that are experienced as being similar by individuals of the study population and should therefore exert similar effects on them, so that a cluster sum score can be assumed to reflect the same amount of a certain kind of experience across participants and time points, even if the exact combination of activities within a given cluster varies over participants or time points. In other words, even if one person plays chess, the other attends a language course, both are assumed to experience the same amount of cognitive stimulation. Or, with respect to time points, if a person stops playing chess and starts a language course instead, this person may experience the same amount of cognitive stimulation at both time points.

1.3.3 Late-life changes in leisure behavior

The activities that older persons chose to engage in are often the same activities they were engaging in earlier in life (Agahi, Ahacic, & Parker, 2006; Janke, Davey, & Kleiber, 2006), which is in accordance with the view that individuals follow the patterns of participation they developed earlier in life, based on long-established needs (Atchley, 1989; Kleiber & Genoe, 2012). Facing health-related limitations, some older adults do also change their patterns of activity engagement, so that on average, leisure activity engagement declines with aging (Agahi et al., 2006; Janke et al., 2006). In addition, a tendency to focus on familiar activities and to not search for novel activities has been suggested to be associated with older age (Iso-Ahola, Jackson, & Dunn, 1994), which is in line with the theoretical model of selective optimization with compensation (Baltes & Baltes, 1990). According to this model, within the given context for a given person, "the process of human development involves an orchestration of selection, optimization, and compensation" (Baltes et al., 1999). Applied to leisure activities in old age, selection could regard goals or outcomes; optimization can be optimizing the means to achieve desired outcomes; and compensation involves a response to loss in goal-relevant means. For example, an older adult facing physical impairments will select the goal of staying active in spite of the impairments. He or she will optimize the choice of activities by dropping (some) physical activities, and compensate the loss of physical activities by engaging more in other activities. The selectivity part of this example can also be described within socio-emotional selectivity theory (Carstensen, 1992), stating that in the face of a limited future time horizon, older adults focus on what induces positive feelings and focus on close relationships with familiar other persons rather than seeking new

relationships, with the goal to seek satisfaction in the present rather than the future (Carstensen, 1992).

1.3.4 Associations between leisure activities and cognitive aging

An association between frequency of engagement in leisure activities and cognitive performance among healthy older adults as well as lower risk for cognitive decline is widely accepted (Fallahpour et al., 2016; Fratiglioni, Paillard-Borg, & Winblad, 2004; Hertzog et al., 2009; Lindenberger, 2014; Stern, 2009; Yates et al., 2016). However, the evidence is mixed, which might be due to differences between studies with regard to design, population, and measures used. A recent review including five small meta-analyses concluded that cognitive leisure activities are associated with reduced risk for future cognitive impairment and dementia (Yates et al., 2016). The meta-analyses included a total 19 studies, divided into groups of studies with different outcome measures. 4 of 5 showed pooled effect sizes reliably in favor for cognitive leisure activities. However, the studies were moderately to substantially heterogeneous in outcome (Yates et al., 2016), limiting the confidence interpretability of the pooled effects. Moreover, studies with widely differing operationalizations of leisure activity engagement were pooled together, which complicates interpretation. Others have therefore refrained from conducting meta-analyses so far (e.g. Fallahpour et al., 2016). In addition to the measures used, the study designs and statistical models used to analyze longitudinal relationships between engagement and cognition vary widely, with clear consequences for the interpretation of the findings (Ghisletta, Bickel, & Lövdén, 2006). An important basic difference to make is whether the observed associations between engagement and cognition are cross-sectional, change-change associations (parallel processes), or some form of dynamic associations. In cross-sectional associations, both variables are measured at the same point in time (as in **Study III**). In change-change associations, both variables are measured several times, and the change in one variable is correlated with the change in the other variable (as in **Study II**). In dynamic associations, at least one of the variables, but ideally both, are measured several times, and the previous value(s) in one variable predict(s) subsequent change in the other variable (**Study IV**). These different patterns of longitudinal associations allow for different conclusions about the underlying causal effects. Cross-sectional associations contain no information about which variable might have an effect on the other, or whether both are the result of a

third process unrelated to the hypothesis. For instance, a cross-sectional association might be the result of engagement before, of cognition before, or both, or might reflect the result of a third process such as high educational level or a cognitively challenging occupation. Change-change associations describe processes that take place at the same time in the same individuals. Thus, they indicate related processes, but do not inform about causal direction or whether third variables account for the association. Positive change-change associations between engagement and cognition indicate that continued engagement might foster preserved cognition, that preserved cognition allows for continuation of engagement, or both. Dynamic associations can give an indication of a direction of causal influence, which is very limited with data from two occasions but can get more informative with data from additional occasions, allowing for lead-lag associations to be modeled. In the following I will review studies in these categories, with a focus on longitudinal studies. Cross-sectional studies have shown associations between leisure activities and cognition in young and old adults (Boraxbekk, Salami, Wahlin, & Nyberg, 2016; Ferreira, Owen, Mohan, Corbett, & Ballard, 2015).

1.3.4.1 Change-change associations between leisure activity engagement and cognitive performance

In a coordinated analysis of four longitudinal studies using multilevel linear mixed models with a time-varying covariate, Lindwall and colleagues (2012) observed change-change relationships between physical activity and cognitive performance in some but not all cognitive domains. Most consistently, change in physical activity was related to change in reasoning (in 4 of 4 studies), less so to change in fluency (2 of 3 studies), memory (2 of 4 studies), and semantic knowledge (2 of 4 studies). Two earlier studies that investigated change-change associations between physical activity and cognition differentiated between duration and intensity of activity (Angevaren, Vanhees, Nooyens, Wendel-Vos, & Verschuren, 2010; van Gelder et al., 2004). Both found stronger associations between intensity and cognition than between duration and cognition.

Concerning intellectual activities, a coordinated analysis of data from the same four observational studies showed change-change associations between engagement in cognitive activities and cognitive performance in all of the studies. Change in cognitive activities was related to change in semantic knowledge (4 of 4 studies), reasoning (3 of 4 studies), memory (3 of 4 studies), and fluency (2 of 3 studies). Two earlier

publications, both from the Victoria Longitudinal Study (VLS), report associations between change in mental activities and change in cognition, here in processing speed (Bielak, Hughes, Small, & Dixon, 2007) and working memory (Hultsch, Hertzog, Small, & Dixon, 1999).

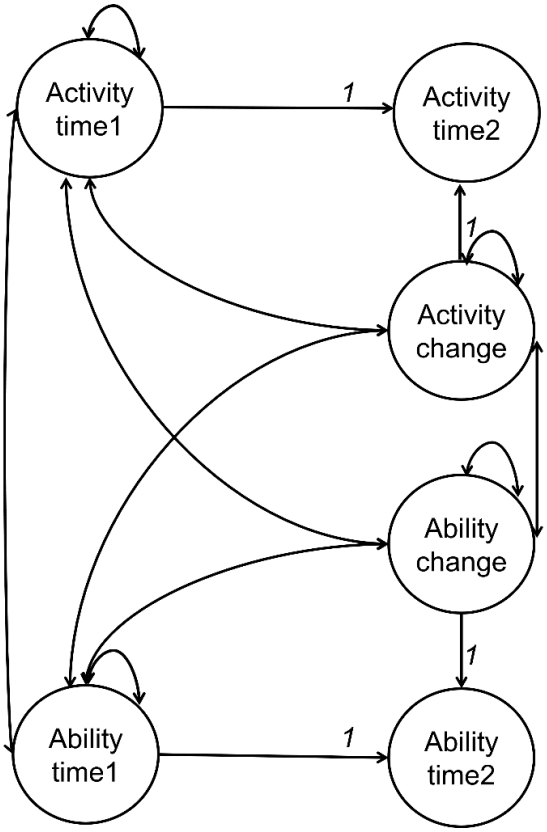

Figure 8: Illustration of a bivariate latent change score model. Two latent change score models (Figure 4) are fitted in the same SEM, and the covariance between levels, change scores, and all level-change covariances are estimated. This model can be used to describe parallel processes.

In a coordinated analysis parallel to Lindwall et al. (2012) and Mitchell et al. (2012), Brown et al. (2012) found change-change relationships between social activities and cognition for reasoning (3 of 4 studies), fluency (2 of 3 studies), memory (3 of 4 studies), and semantic knowledge (1 of 4 studies). Overall, the evidence is thus somewhat weaker for change-change associations between engagement in social activities and cognition than for engagement in physical or mental activities and cognition. However, for reasoning, fluency and memory, there were still more studies that showed a significant association than those that did not. Earlier publications from the VLS also included social activities but found no significant change-change associations between social activities and cognition (Bielak et al., 2007; Hultsch et al., 1999). Windsor and colleagues (Windsor, Gerstorf, Pearson, Ryan, & Anstey, 2014) analyzed data on social

interactions from the PATH through life project, which yielded mixed results.

To conclude from correlated-changes studies, using a similar design as we do in **Study II** (Figure 8), there is some reason to believe that changes in physical, mental, and social activity as well as social support and social interaction are associated with changes in cognition in old age. Associations have been found for different types of activities and different cognitive domains, but it is not yet possible to conclude about whether such associations are stronger for some types of engagement or specific cognitive domains.

1.3.4.2 Dynamic longitudinal associations between engagement and cognition

Positive associations between habitual *physical* activity at one point in time and subsequent cognitive change have been observed in numerous observational studies (Bauman, Merom, Bull, Buchner, & Singh, 2016; Blondell, Hammersley-Mather, & Veerman, 2014; Boraxbekk et al., 2016; Memel, Bourassa, Woolverton, & Sbarra, 2016; Prakash, Voss, Erickson, & Kramer, 2015; Sofi et al., 2011; Willey et al., 2016). Many studies that included *mental* activities found a relationship of these with changes in cognition (Fallahpour et al., 2016; Iwasa et al., 2012; Kåreholt, Lennartsson, Gatz, & Parker, 2011; H. X. Wang et al., 2013; Vaughan et al., 2014; R. S. Wilson et al., 2003; Yates et al., 2016), but not all studies did (Mitchell et al., 2012), and the studies that did differ in many respects. Studies analyzing associations between *social* activities at baseline and subsequent change in cognition have yielded mixed results (Iwasa et al., 2012; Newson & Kemps, 2005; H. X. Wang et al., 2013). The exact classification of single leisure activities as "social" varied widely between studies, so that the specificity of the association with "social" activities remains questionable.

1.3.4.3 Studies with lead-lag models

Lead-lag models allow to simultaneously estimate influences in both directions. Based on several repeated measurements of both engagement and cognition, they can test whether the influence of engagement on subsequent change in cognition is stronger or weaker than the influence of cognitive performance on subsequent change in activity engagement. Studies that investigate lead-lag relationships are still rare and those available yield a mixed pattern of results, each of them finding associations for some types of activities and not others or some cognitive domains but not others (Ghisletta

et al., 2006; Lövdén, Ghisletta, & Lindenberger, 2005; Mousavi-Nasab, Kormi-Nouri, & Nilsson, 2013; Small, Dixon, McArdle, & Grimm, 2012).

1.3.4.4 Intervention studies

Although it is difficult to randomly assign persons to lifestyles, recent attempts to intervene with lifestyle in general (Miia Kivipelto et al., 2013), or with certain leisure activities, in randomized controlled trials (RCT; Park et al., 2014; Stine-Morrow, Parisi, Morrow, & Park, 2008) obtained somewhat promising results. In the Finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER), a RCT based on about 1200 elderly individuals at risk for cognitive decline. The lifestyle intervention comprised of nutritional counseling, physical exercise, psycho-education and computer-based cognitive training and resulted in small, but significant intervention effects in executive functions and perceptual speed. Both the intervention group and the control group had increased cognitive performance after 12 months and further increased performance after 24 months. The two groups differed by .05 to .06 standard deviations in cognitive test performance after 24 months (Ngandu et al., 2015). In an intervention more focused on cognitively stimulating leisure activities, the Synapse project, 221 participants completed a 3-months program with an average of about 16 hrs of activity per week (Park et al., 2014). They were randomly assigned to either cognitively demanding activity groups or non-demanding activity groups. In the demanding activity groups, they learned quilting, photography, or both. In the non-demanding activity group they engaged in facilitator-led social interactions and group entertainment, or in low-demand "placebo" cognitive activities (such as listening to classical music). At post-test, the high cognitive demand groups had significantly higher memory scores than at pretest than the low cognitive demand groups, with a post-test group difference of about .25 standard deviations (Park et al., 2014).

Exercise intervention studies have documented positive effects of exercise on cognitive performance in healthy elderly persons across studies and several meta-analyses (Ahlskog, Geda, Graff-Radford, & Petersen, 2011; Carvalho, Rea, Parimon, & Cusack, 2014; Düzel, van Praag, & Sendtner, 2016; Jonasson et al., 2016; Liu-Ambrose et al., 2008; Maass et al., 2015; P. J. Smith et al., 2010; Voss, Carr, Clark, & Weng, 2014) as well as in dementia patients (Farina, Rusted, & Tabet, 2014; Groot et al., 2016; Heyn, Abreu, & Ottenbacher, 2004; but see Forbes, Thiessen, Blake, Forbes, & Forbes, 2014). However, two Cochrane meta-analyses with rather strict

criteria on study inclusion do not conclude that aerobic exercise is beneficial for healthy adults (Young, Angevaren, Rusted, & Tabet, 2015) and that exercise programs for dementia patients are supported by the evidence (Forbes, Thiessen, Blake, Forbes, & Forbes, 2014).

Cognitive training studies imply that cognitive ability in old age is malleable and can be influenced by individual training. However, even though more and more studies are conducted, most are small-scale studies with considerable variance in regard to training paradigm, trained abilities, outcome measures, and to whether their control group was active ("placebo" training) or passive (no contact). Meta-analyses (Bahar-Fuchs, Clare, & Woods, 2013; Martin, Clare, Altgassen, Cameron, & Zehnder, 2011; Papp, Walsh, & Snyder, 2009; Reijnders, van Heugten, & van Boxtel, 2013; Valenzuela & Sachdev, 2009) are thus to be interpreted with care. An important issue in evaluating training effects is the presence or absence of transfer effects, that is, whether or not trained participants improve their performance not only in the trained tasks or very similar tasks but also in other types of tasks or even other abilities. When applied to leisure activities, the issue is whether engaging in a certain activity can be expected to increase cognitive abilities that are not directly related to the given activity. A recent meta-analysis (Karbach & Verhaeghen, 2014) with relatively homogeneous set of included studies focused on training of working memory documented net training effects (gains in the training group minus gains in the control group) of 0.5 standard deviations for near transfer (same ability, different test) and of 0.2 standard deviations for far transfer (different ability). While this is promising, more evidence is still needed to confirm this.

1.3.4.5 Conclusion on activity engagement and cognition

To conclude, observational studies are so heterogeneous that it is premature to summarize the evidence on activity engagement and cognition in terms of a meta-analysis. However, bearing the differences in mind, overall, a large number of studies have been conducted that indicate that some type of leisure activity is related to cognitive change in late life. Intervention studies both on physical exercise and cognitive training show promising results, but need also to be backed up by further evidence.

1.3.5 Relative importance of leisure activities for predicting cognitive change

Across studies, the observed associations between engagement in leisure activities and change in cognition are weak to moderate, raising the question

of how important activity engagement really is. When a wide range of predictors of cognitive change are combined in linear models, only a relatively small portion of the variance can be accounted for by engagement (Albert et al., 1995; S. J. Ritchie et al., 2016). Such linear models however have the limitations that non-linear predictor effects and interactions among predictors are not considered, as long as they are not explicitly pre-specified in the regression model. Interactions among many of the potential predictors are however likely to be common but difficult to specify when the number of predictors is large. For example, several studies report stronger positive associations of physical activity and cognitive performance for individuals carrying risk alleles for Alzheimer's disease (Ferencz et al., 2014; Rovio et al., 2005; Schuit, Feskens, Launer, & Kromhout, 2001; 2012).

Instead of using linear models, non-parametric approaches to classify persons into groups with different trajectories according to lifestyle variables and related characteristics that might be informative in this context. This can be done using decision-tree based methods such as SEM trees (Brandmaier, von Oertzen, McArdle, & Lindenberger, 2013). This technique combines a pre-defined and theoretically motivated structural equation model with decision trees, such that it recursively (that is, over and over again) splits the data into two partitions according to the most informative predictor chosen from a set of candidate predictors. In contrast to linear models, in which non-linear effects and interactions need to be pre-specified, the exploratory nature of the SEM trees allows the relationship between a predictor and the outcome to follow any functional form and interactions can be detected without being pre-specified. We complemented the SEM tree analysis with the more recently developed SEM forests (Brandmaier, Prindle, McArdle, & Lindenberger, 2016), an application of the idea of random forests (Breiman, 2001) to SEM trees. As a complement to single trees, forests provide additional insights while building upon the same principles. SEM forests are ensembles of SEM trees, in which each tree is based on a randomly drawn subsample of the participants and each split within the trees is based on a random subset of predictors. From a SEM forest, for each predictor, a summary measure of the predictor's importance across trees can be derived. This measure, *variable importance,* subsumes both the main effect of a predictor and its interaction effects with other predictors on the outcome. It is a relative measure and reflects the importance of the predictor compared to other predictors in the set. The fact that predictor-outcome relationships need not to be linear, and the fact that interactions are implicitly captured in the variable importance are both

crucial reasons for us to apply this method. It is conceivable that the potential benefit of leisure activity engagement depends upon many factors and circumstances, such as retirement status (Ihle et al., 2016), pre-retirement work characteristics (Andel, Finkel, & Pedersen, 2016), or genetic predispositions (Ferencz et al., 2014; Niti, Yap, Kua, Tan, & Ng, 2008).

As a newly implemented feature of SEM forest, the *partial dependence* of an outcome parameter on a given predictor can be computed. It measures the marginal association between the predictor and the outcome, all links to other predictors being averaged out. SEM trees and forest are newly developed techniques, but have been used to explore multi-indicator constellations of physical health and psychosocial correlates of terminal decline in wellbeing (Brandmaier, Ram, Wagner, & Gerstorf, in press) and to explore psychosocial and health-related predictors of inter-individual differences in episodic memory performance (Brandmaier et al., 2016).

In **Study IV**, we use SEM trees and forests to assess the importance of leisure activities relative to other predictors of inter-individual differences in change in perceptual speed.

1.4 LEISURE ACTIVITIES AND BRAIN STRUCTURE

1.4.1 White matter microstructure

White matter microstructure in the brain changes with experience (Fields, 2010; Lövdén, Bodammer, et al., 2010; Mackey, Whitaker, & Bunge, 2012; Scholz, Klein, Behrens, & Johansen-Berg, 2009; Zatorre et al., 2012). Cognitive training brings about changes in white matter microstructure that can be interpreted as greater structural integrity (Lövdén, Bodammer, et al., 2010; Mackey et al., 2012), thus, white matter microstructure shows plasticity. Physical fitness has also been related to white matter microstructure (Gons et al., 2013; Voss et al., 2013), which may reflect the sensitivity of white matter structure to vascular problems (Wang et al., 2015). In **Study II,** we investigated whether change in change in white matter microstructure associated to change in both engagement and perceptual speed statistically accounts for an association between the two, in persons 81 and older.

1.4.2 Dopamine D2 receptors

Physical exercise also affects the brain's DA system (Lin & Kuo, 2013). Only few studies on physical activity and DA have been conducted with human participants – all of them were patient studies. A recent exercise

intervention study in humans documented increased $D_{2/3}$DR BP in abstinent methamphetamine users that completed an 8-week exercise training program s compared to a control group with the same diagnosis (Robertson et al., 2016). This study suggests that striatal dopaminergic deficits related to methamphetamine addiction might be ameliorated by physical exercise. Epidemiological studies have found associations between physical activity and reduced risk for PD (Chen, Zhang, Schwarzschild, Hernan, & Ascherio, 2005; Thacker et al., 2008; Xu et al., 2010), suggesting a protective effect of physical activity on DA integrity.

Animal studies clearly suggest a link between exercise and DA. An early study found enhanced [3H]spiperone binding at D2/3DR's in striatal post-mortem tissue of rats that had completed 12 weeks of motorized treadmill training as compared to control rats (Gilliam et al., 1984). Furthermore, endurance training increased D2DR density in striatum of rodents in another study using the same marker and measuring DA levels and metabolites (MacRae, Spirduso, Walters, Farrar, & Wilcox, 1987). A recent study in rats demonstrated that the beneficial effect of voluntary exercise on learning was disrupted by infusion of a D2-antagonist into the striatum (Eddy, Stansfield, & Green, 2014), suggesting D2 receptor-dependent signaling in striatum as a mediator of exercise-related effects on cognition in these animals. Also, cortical DA levels are elevated after four weeks of running-wheel exercise in wild-type rats, but not in animal models of Huntington's disease in which the DA system is disrupted (Renoir, Chevarin, Lanfumey, & Hannan, 2011). Animal studies of Parkinson's disease (PD) show that exercise decreases symptoms and counteracts the detrimental effects of neurotoxins that are used to induce the disease in the animal models (Gerecke, Jiao, Pani, Pagala, & Smeyne, 2010; Mabandla, Kellaway, Gibson, & Russell, 2004; Tajiri et al., 2010; Yoon et al., 2007). Thus, at least for physical activity, DA functioning may be related to activity engagement. This issue is examined using cross-sectional data on inter-individual differences in persons in their mid-60s.

2 AIMS

The general aim of this thesis is to further our understanding of how and why leisure activity engagement is related to aging-related changes in cognitive performance.

Specifically, I sought to…

A. identify components of lifestyle, especially within leisure activities, that are associated with late-life cognitive performance (**Studies II-IV**),
B. identify brain correlates of these lifestyle components that are also relevant for cognitive performance (**Studies I-III**), and
C. explore the relative importance of lifestyle- and health-related factors, including interactive effects, on change in cognition (**Study IV**).

3 DATABASES

3.1 THE SNAC-K STUDY

Studies I, II, and IV are based on data from the ongoing longitudinal population-based Swedish National study on Aging and Care – Kungsholmen, SNAC-K (Lagergren et al., 2004), that started in 2001. The goals of SNAC-K are to "understand the aging process, and to identify possible preventive strategies to improve health and care in elderly adults" (www.snac-k.se).

3.1.1 Participants

For SNAC-K, 5,111 inhabitants of the Kungsholmen island in central Stockholm were randomly selected from pre-specified age cohorts and invited to take part in the study. The age groups were 60, 66, 72, 78, 81, 84, 87, 90, 93, 96, and 99+ years, and the age groups 60, 66, and 90+ were oversampled. Of those invited, 4,590 were alive and eligible, and 3,363 of them took part in the baseline assessments between 2001 and 2004. The main reason for not participating was refusal (*n* = 1,164, 25%), followed by refusal by relative (*n* = 61, 1%), and disrupted examination (*n* = 2, 0.004%). Selectivity with regard to age ($M_{effective}$ - M_{total})/ SD_{total}) was negligible (0.03 SD). The assessments consist of a nurse interview, a medical examination, and a neuropsychological testing session and take around 6 hours in total. Participants are re-examined when they reach the age of the next age cohort; that is, up to age 78, they are re-examined after 6 years, and after age 78, they are re-examined after 3 years. 2,848 persons participated in neuropsychological testing. Reasons for not participating were refusal (n = 390, 12%), low Mini-Mental-State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) score (<10, *n* = 106, 3%), death (*n* = 10, 0.3%), and other (*n* = 9, 0.3%). Selectivity with regard to gender distribution, age and MMSE scores was small (0.05– 0.08 SD's; Laukka, Lövdén, Herlitz, et al., 2013).

In **Studies I** and **II**, we included only data from the first and second follow-up assessments, due to the fact that longitudinal DTI data were available only from these occasions. At first follow-up, 764 individuals underwent neuropsychological testing. Of these, we excluded persons with a dementia diagnosis (*n* = 196), Parkinson's disease (*n* = 2), or Guillain-Barré syndrome (*n* = 1) at first or second follow-up, resulting in 563 participants in **Study I** with data on cognitive abilities at first follow-up. For **Study II**, we

restricted the sample further to those who had data on cognition *and* leisure activities available at first follow-up, resulting in an effective sample of 450 participants. For the second follow-up, we had cognition data on 378 persons in **Study I** and 325 persons in **Study II**.

3.1.2 Assessment of cognitive performance

The neuropsychological testing took 1½ hours to complete and included an extensive cognitive test battery, administered by trained psychologists according to a standardized procedure. The tasks were administered in two different orders so that effects of fatigue on a specific task could be minimized. The tests were also administered in three different versions to avoid retest-effects in the longitudinal analyses. Of the cognitive tests administered, the studies included in this thesis focused on perceptual speed. (For measures of the other cognitive abilities in SNAC-K, please see Study I and Laukka et al., 2013). Perceptual speed tasks comprised two paper-pencil tests. One was a digit cancellation task where participants were asked to cross every "4" in a random sequence of digits as quickly as possible (Zazzo, 1974). Performance was measured as the number of correct answers within 30 seconds. The second task was a pattern comparison task (Salthouse & Babcock, 1991), in which participants were instructed to go through pairs of line-segment patterns and mark as fast as possible whether the two items of a pair were "same" or "different". Performance was measured as number of correctly classified pairs achieved in 30 seconds. The test consisted of 2 pages of pattern pairs, the participants obtained a score for each page, and the final performance score was the mean of the two scores.

3.1.3 Assessment of leisure activities and lifestyle

Leisure activities were assessed with a self-administered questionnaire consisting of a list of 26 activities. Participants reported how often they engaged in each activity during the last 12 months. Response categories were analyzed as a continuous score (0 = "never", 1 = "more rarely than every month", 2 = "every month", 3 = "every week", missing = "I don't know"). We conducted a rating study with 68 participants (72-93 years) from a later wave of the SNAC-K study who volunteered to fill in an extra questionnaire about the activities' characteristics. Each activity's intellectual, physical and social component was rated on a 4-point scale. The raters provided ratings only for those activities they had pursued themselves during the last 12 months, so that ratings were based on their own recent

experience. For **Study II,** we used the ratings of raters aged 78 years and older, and for **Study IV**, we used data from all raters. In both studies, we averaged a rating for each activity across raters. A hierarchical cluster analysis (based on Euclidean distances, Ward's method; Ward, 1963) was performed on the mean ratings for the three components across persons. To assess how well a given cluster solution fitted the data, multiscale bootstrapping was done with the package pvclust (Suzuki, 2006) in R (RCoreTeam, 2016).

In **Study II**, the clustering resulted in four clusters. The first cluster included activities that were rated rather low on physical and mental demand and high on social components, such as going to the cinema, concert, or theatre. We labelled it predominantly social, as the social component was most prominent. The second cluster comprised activities with a more complex profile, that is, a higher physical and mental demand but also a high social component, such as traveling. We labelled it complex. The third cluster contained activities with relatively high physical demands, low mental demands, and medium social component, such as gardening. We labelled it predominantly physical, but note that the included activities are not necessarily highly physically demanding. The fourth cluster incorporated activities with rather low scores on all 3 rating dimensions, such as watching TV. We therefore labelled it low level.

In **Study IV**, we obtained five clusters from the cluster analysis, which we labelled "social activities" (high rating on the social component), "physical activities" (high ratings on the physical component), "intellectual-social activities" (high ratings on the intellectual and social components), "complex activities" (high ratings on all three components), and "intellectual-solitary activities" (medium ratings on intellectual, low ratings on the other components).

In both studies, each SNAC-K participant's report on how often he or she engaged in each activity was summed up across activities within each rating-based cluster. The rationale behind the clustering of the activities and using cluster sum scores as predictors of cognitive decline is as follows: The clustering shows us which activities share similar characteristics, that is, which activities show a similar combination of physical, social and intellectual components. Rather than being interested in possible effects of specific activities, we are interested in the effects of the underlying component. Given that activities within each cluster are similar with regard to their component structure, they should be interchangeable in their effect on the individual and can thus be aggregated.

In **Study IV**, we included another measure of physical activity, as it was assessed with two specific questions in the questionnaire. The first question concerned how often a participant engaged in low-intensity physical activity (walks on the sidewalk or paved surfaces, in parks, in forests, short bike rides, light aerobic activities or gym classes, golf), and the second question asked about moderate to intense exercises (brisk walking, jogging, heavy gardening, long bike rides, intense aerobic activities or gym classes, skating, skiing, swimming, ball games or similar activities). The response categories were "every day", "several times a week", "2-3 times/month", "less than 2-3 times/month", and "never". We categorized participants into three groups that reflect their adherence to the recommendations by the World Health Organization (WHO, 2010): "inadequate": less than 2–3 times per month in light and/or moderate/intense exercise; "health enhancing": light exercise several times per week or every day; and "fitness-enhancing: moderate/ intense exercise several times per week or every day (Rydwik et al., 2012).

3.1.4 Assessment of further covariates

In all studies, we used age, education, and sex as covariates. In **Study IV**, we included a wider range of variables as predictors of change in perceptual speed, because they had been shown to be related to perceptual speed, or we assumed them to interact with leisure activities in predicting change in perceptual speed. We included information on *ApoE*, which was derived from blood samples taken at baseline assessment (Laukka et al., 2013). We also included also the personality traits Extraversion, Neuroticism, and Openness, which had been assessed using a questionnaire (NEO-FFI) (Costa & McCrae, 1989). Data on retirement status (retired/ not-retired), self-reported measures of social interaction frequency and social network size were also used. Finally, we included the cardiovascular risk factors smoking, hypertension, body mass index (BMI), cholesterol level, and diabetes. In addition, as a measure of general health, we included number of chronic diseases (Calderón-Larrañaga et al., 2016), and as a proxy for physical functioning, we used walking speed (Welmer, Rizzuto, Qiu, Caracciolo, & Laukka, 2014). For details of the assessment of these variables, see **Study IV**.

3.1.5 MRI/ DTI acquisition and preprocessing

All MR images were obtained using the same 1.5 T scanner (Philips Intera, Netherlands). Because of a change in the DTI scanning sequence between

baseline and first follow-up assessment, the data from baseline assessment could not be used in a longitudinal data analysis. We therefore used DTI data from the first and second follow-up occasion in SNAC-K for **Studies I** and **II**. At first and second follow-up, DTI data were acquired using a single-shot diffusion-weighted echoplanar imaging sequence with the following parameters: FOV = 230 × 138 mm^2; 128 × 77 matrix; TE = 104 ms; TR = 5368 ms; and slice thickness = 5 mm with 1 mm gap. One volume of non-diffusion-weighted images (b = 0) and 6 volumes of diffusion-weighted images at a b-value of 600 s/mm2 were acquired. The DTI scheme was composed of 6 noncollinear gradient directions. T1-weighted images were acquired using the 3D FFE (fast field echo) sequence. The acquisition parameters were: TR = 15 ms, TE = 7 ms, flip angle = 15°, number of slices (axial) = 128, slice thickness = 1.5 mm, in-plane resolution = 0.9375 × 0.9375 mm, no gap, FOV=240 × 240, and matrix=196 × 256.

The preprocessing of DTI data is described in detail in **Study I**. In brief, it included correction for eddy current artifacts and motion and calculation of the tensor elements. FA and MD were derived on a voxel-by-voxel basis (Lövdén et al., 2012). The FA data were submitted to tract-based spatial statistics (TBSS; S. M. Smith et al., 2006), normalized, and thinned to create a mean FA skeleton, which represents the centerlines of all tracts common to all participants. The mean skeleton was then thresholded and binarized at FA > .2, which resulted in a thin skeleton that included 101466 voxels. Each participant's normalized FA and MD data were then projected onto this skeleton. From the individual skeleton images, we extracted mean FA and MD for six ROIs in each brain hemisphere, that is cingulate gyrus part of cingulum (CCG), the corticospinal tract (CS), the forceps major (FMAJ), the forceps minor (FMIN), the inferior fronto-occipital fasciculus (IFOF), and the superior longitudinal fasciculus (SLF). The ROIs were defined according to the JHU white matter tractography atlas (Wakana, Jiang, Nagae-Poetscher, Van Zijl, & Mori, 2004), and the Catani tractography atlas (Catani & De Schotten, 2008).

3.1.6 Ethical considerations

The SNAC-K project complies with the declaration of Helsinki and was approved by the ethical committee at Karolinska Institutet (baseline data collection: 01-114), and the regional ethical review board (follow-up data collections: 04-929/3, Ö 26-2007). Participants provided informed consent. In case a participant was cognitively impaired (MMSE ≤ 22), informed consent was obtained from next-of-kin.

3.2 THE COBRA STUDY

The Cognition, Brain, and Aging (COBRA) study is a longitudinal multimodal imaging study designed to obtain knowledge about aging-related changes in the brain and associated changes in cognition. Specifically, COBRA seeks to document longitudinal changes in D2DR availability, grey and white matter integrity and functional brain activation, to examine longitudinal brain-cognition associations, to assess the temporal dynamics of different changes in the brain, and to chart genetic and lifestyle factors associated with brain and cognitive aging (Nevalainen et al., 2015).

3.2.1 Participants

The COBRA participants were randomly drawn from the population registry in Umeå, a medium-sized city in northern Sweden, in the pre-defined age range of 64-68 years at study enrollment. Invited were all persons that did not meet the following exclusion criteria: past or present history of brain trauma or stroke, dementia, intellectual disability, functional impairment or movement disorders, epilepsy, psychological disorders, diabetes, ongoing malignancy treatment, functional or auditory impairments, severely reduced vision, claustrophobia, expected difficulties to lie still during the 1 h scanning session, poor Swedish language skills, and presence of metal in the body (Nevalainen et al., 2015). Of 590 persons invited, 219 agreed to participate. Of these, 29 dropped out before the first session and five after the first session, and two were excluded based on newly discovered brain tumor and two based on newly diagnosed diabetes. The resulting effective sample of 182 persons consisted of relatively highly educated individuals, compared to the general population in Sweden (43.6% of the participants had an educational attainment exceeding high school degree, compared to 17.5% in the general Swedish population).

3.2.2 Assessment of cognitive performance

Participants underwent extensive computerized tests in the cognitive domains of working memory, episodic memory, and perceptual speed. The tests were developed in the context of the COGITO study (Schmiedek, Lövdén, & Lindenberger, 2010), and adapted for the use in COBRA (Nevalainen et al., 2015). Each of the three cognitive domains is tested with three tasks, of which one was based on verbal, one on numerical, and one on spatial/figural material (Schmiedek et al., 2010).

Episodic memory was assessed with a word recall task, a number-word recall task, and an object-position recall task. For word recall, participants were presented with 16 Swedish words appearing one after one for 6 s each, with an inter-stimulus-interval (ISI) of 1 s. The words were concrete, easy to spell, and easily distinguished. After having seen all words, participants typed them in any order. For number-word recall, participants were presented with 2-digit numbers paired with concrete plural nouns. Eight pairs were shown for 6 s each, with an ISI of 1 s. Participants were prompted with a question for the number to the noun, one at the time, and typed the number on the keyboard. In the object-position task, participants were presented with a grid of 6 x 6 squares in which, 12 objects appeared consecutively at different locations, for 8 s each, with an ISI of 1 s. At test, all objects were presented next to the grid and participants moved them to the remembered location, using the computer mouse. In each of the episodic memory tasks, performance was measured as the sum of correctly identified items across two consecutive test trials, which were preceded by a practice trail for each task.

Working memory was tested with a letter-updating task, a numerical 3-back task, and a spatial updating task. In letter-updating, a sequence of letters (A-D) was presented on screen (1 s, ISI = 0.5 s) and participants were instructed to continuously remember the last three letters shown and were, at 16 random points in the presentation, requested to type the last three letters. The numerical 3-back task was a columnized version of n-back, where a row of 3 boxes was visible on screen, and in each box, one at a time and starting from the left, a digit was presented (1.5 s, ISI = 0.5 s). After a number appeared in the right box, the next followed in the left box. Participants were instructed to indicate whether or not a number appearing in a specific box was the same as the last number displayed in that particular box (by pressing a key for “yes” or “no” for each number). Four trials with 30 numbers each were run. For spatial updating, participants were presented with 3 separate 3x3 grids next to each other. Three circles, one in each grid, were presented for 4 s. Then, an arrow appeared beneath each grid (one at the time, ISI 0.5 s) indicating in which direction each circle should be mentally moved. This was done twice for each grid, after which the participants should indicate the updated locations of the circles. 10 trials were run. In all working memory tasks, correct answers across trials was taken as the performance score.

Perceptual speed was assessed with a letter-comparison task, a number-comparison task, and a figure-comparison task. In each of these

tasks, participants had to compare two items simultaneously presented on the screen and press a button for “same” or “different” as quickly as possible. For letter comparison, 4-letter strings had to be compared. Two trials with 40 string pairs each were run, half of the string pairs being identical. A score for correct responses per minute was calculated. For number comparison, the strings consisted of 4 digits, and for figure comparison, participants were presented with two abstract figures to compare.

3.2.3 Assessment of leisure activities and lifestyle

We used an activity questionnaire designed for the purpose of the COBRA study and tailored to life in northern Sweden. This questionnaire included 43 activities, chunked into the categories of intellectual, physical, and social activities. Participants were asked to indicate for how many hours (options: 1-14 h with 1-h increments, or 15+ hrs) they would engage in each of the activities during a typical summer week. Summer was taken as a reference season because the opportunities for various kinds of activities differ largely across seasons in northern Sweden. In addition, for physical activities, participants were asked to indicate how physically demanding it normally is for them to perform the activity. For mental activities, it was asked how mentally demanding the activity normally is for them.

3.2.4 PET imaging and BP_{ND} calculation

All participants underwent a PET scan (Discovery PET/CT 690; General Electric, WI, US) following an intravenous bolus injection of 250 MBq [11C]raclopride. Following the bolus injection, a 55-min 18-frame dynamic scan was acquired with the participants resting in the scanner. Attenuation- and decay-corrected PET images (47 slices, field of view = 25 cm, 256 × 256-pixel transaxial images, voxel size = 0.977 × 0.977 × 3.27 mm^3) were reconstructed, PET scans were corrected for head movements, and co-registered to the corresponding MRI image using Statistical Parametric Mapping software (SPM8)(Ashburner et al., 2013). $D_{2/3}$DR binding potential to non-displaceable tissue uptake (BP_{ND}) was calculated with Logan analysis (Logan et al., 1996) based on time-activity curves for caudate, putamen, hippocampus and cerebellum. Grey matter in cerebellum was used as a reference region due to its negligible $D_{2/3}$DR expression (Farde, Hall, Ehrin, & Sedvall, 1986).

3.2.5 Ethical considerations

The COBRA study is conducted in accordance with the Declaration of Helsinki. The study was approved by the Regional Ethical board and the local Radiation Safety Committee of Umeå, Sweden (Dnr 2012-57-31M). We obtained written informed consent from all participants prior to testing.

Table 1: Overview of the four studies included in this thesis

Study	Study design & analysis	Lifestyle components	Brain correlates	Cognitive domains	Main results
I	Longitudinal, 3-year change-change links; SEM, linear associations		White matter microstructure in 6 tracts of interest	Perceptual speed, episodic memory, semantic memory, letter fluency and category fluency	Change in white matter microstructure in the cortocospinal tract is associated with change in perceptual speed
II	Longitudinal, 3-year change-change links; SEM, linear associations	Frequency of engagement in leisure activity in the clusters predominantly social, complex, predominantly physical, and low-level	White matter microstructure in the corticospinal tract	Perceptual speed	Change in predominantly social activities is related to change in white matter microstructure in the corticospinal tract and perceptual speed
III	Cross-sectional; SEM, linear associations	Frequency and subjective intensity in physical activity	Dopamine D2 receptor availability	Perceptual speed, episodic memory and working memory	Subjective intensity of physical activity is related to dopamine D2 receptor availability in caudate nucleus, episodic memory and working memory
IV	Longitudinal, level of predictor – 6-year change in outcome; SEM-trees and forests, associations can be non-linear, interactions also represented in variable importance measure	As predictor: Frequency of engagement in leisure activity in the clusters social, intellectual-social, intellectual-solitary, complex. Physical activity level		As outcome: Change in perceptual speed	Leisure activity clusters show similarly high variable importance and were more important than physical activity, but less important than age, retirement, walking speed, and multimorbidity

4 SUMMARIES OF STUDIES

4.1 STUDY I: CHANGES IN PERCEPTUAL SPEED AND WHITE MATTER MICROSTRUCTURE

4.1.1 Background

White matter microstructure is related to neural information transmission and synchronous processing in large-scale neural networks (Andrews-Hanna et al., 2007; Fields, 2008). Cross-sectional brain imaging studies using DTI have demonstrated differences in white matter microstructure between younger and elderly persons (Madden et al., 2012; O'Sullivan et al., 2001; Sullivan & Pfefferbaum, 2006), we hypothesized that age-related changes in white matter microstructure might constitute a neural underpinning of age-related changes in cognitive performance. One previous longitudinal study shows change-change associations between whole-brain MD and working memory, but not perceptual speed or executive functions (Charlton et al., 2010). This study did not examine regional differences in these associations, i.e. whether change in cognition is related to specific white matter tracts. However, inter-individual differences in white matter microstructure are to some extent regionally specific (Lövdén et al., 2012; Penke, Maniega, Murray, et al., 2010). We extended previous research by investigating change-change relationships between white matter microstructure in various brain regions and performance in different cognitive domains.

4.1.2 Method

4.1.2.1 Participants

We included 563 participants from the first and second follow-up of the neuropsychological testing in SNAC-K. Participants were 81 years or older at the first follow-up occasion (age: M = 85.4 years, SD = 4.6). The second follow-up of took place about 3 years later (time between neuropsychological testing occasions: M = 2.7 SD = .3 years) and 378 of the participants returned. Of the 563 persons that had taken part in neuropsychological testing at first follow-up, 77 had undergone DTI scanning yielding data of sufficient quality. At second follow-up of DTI scanning (after M = 2.3, SD = .2 years), 40 of these returned and were tested again.

4.1.2.2 Measures and data analyses

We extracted mean FA and mean MD from six ROIs that represent the brain's largest white matter tracts. We used SEM to model inter-individual differences in cognitive performance and white matter microstructure. Specifically, we defined LCM to assess inter-individual differences in intra-individual change. In a series of bivariate LCM, performance level and change in each cognitive domain (perceptual speed, episodic memory, letter fluency, category fluency) was combined with FA /MD level and change in each white matter tract (CCG, CS, FMAJ, FMIN, IFOF, SLF).

4.1.3 Results

On average, in major white matter tracts, FA decreased and MD increased over the follow-up period. Inter-individual differences in change of FA were significant for five of the six examined tracts. Inter-individual differences in MD change were significant for three of the tracts. Individual differences in FA change were associated across tracts. By contrast, MD changes were weakly associated among tracts, and generally also correlated weakly with FA changes. Mean longitudinal decline was also observed for the investigated cognitive abilities. Importantly, decreases of perceptual speed were highly correlated with both decreases in FA and increases in MD in the CS tract.

4.1.4 Conclusion

Decreasing FA and increasing MD may indicate deterioration in white matter microstructure, which can be expected to be seen in late life (Fields, 2008). In participants aged 81 years and older, inter-individual differences in these microstructural changes were related to inter-individual differences in perceptual speed changes. This change-change correlation suggests that the CS tract is a neural underpinning of perceptual speed that is sensitive to changes in old age. The CS tract connects the motor cortex, and to some extent the somatosensory and parietal cortices, with the spinal cord. This pathway has a role in cortical modulation of spinal cord activity and is therefore critical for sensorimotor functions, such as precise voluntary hand and finger movements, which were required for the perceptual speed task in this study (Lemon & Griffiths, 2005). Our findings are in line with cross-sectional studies that report associations between white matter microstructure and level of performance in fluid cognition (Madden et al., 2012; Penke, Maniega, Houlihan, et al., 2010) and perceptual speed

(Laukka, Lövdén, Kalpouzos, et al., 2013; Penke, Maniega, Houlihan, et al., 2010; Salami, Eriksson, Nilsson, & Nyberg, 2012). To conclude, change in white matter microstructure is a feature of brain structure that is closely linked to decline in perceptual speed in late life, likely reflecting the sensorimotor part of perceptual speed performance.

4.2 STUDY II: CHANGES IN LEISURE ACTIVITIES, WHITE MATTER MICROSTRUCTURE, AND PERCEPTUAL SPEED

4.2.1 Background

The brain's white matter microstructure shows experience-dependent changes (Fields, 2010; Lövdén, Bodammer, et al., 2010; Scholz et al., 2009; Zatorre et al., 2012) and changes in white matter microstructure are related to changes in perceptual speed in late life (**Study I**). In **Study II**, we investigated whether aging-related change in white matter microstructure is related to both activity engagement and cognition, and if so, how much of the statistical association between change in activity engagement and change in perceptual speed is shared with white matter microstructure, suggesting white matter microstructure to be a candidate neural underpinning of the effect of activity engagement on perceptual speed.

4.2.2 Method

4.2.2.1 Participants

We included 442 individuals from the second follow-up occasion of the neuropsychological assessments in SNAC-K. Of the 563 participants included in **Study I**, only the 450 who also had completed the self-administered questionnaire about leisure activity frequency were included in **Study II**. In addition, we excluded 8 multivariate outliers. For 70 of the remaining 442 individuals, DTI data were available. At the second follow-up, data on cognition and leisure activity frequency was available for 325 persons, and DTI data for 37 persons.

4.2.2.2 Measures and data analyses

As a measure of white matter microstructure, we focused on FA and MD in the CS tract because we had previously found that only changes in this tract are significantly associated with changes in perceptual speed in the current sample (**Study I**). As white matter hyperintensities (WMHs) are related to both white matter microstructural changes (Maniega et al., 2015; Vernooij

et al., 2009) and perceptual speed (Longstreth et al., 2005; S. J. Ritchie et al., 2015; Vernooij et al., 2009), we also controlled for global WMH volume in additional analyses.

As in **Study I**, we employed bivariate LCM to investigate the associations among levels and changes in FA and MD in the CS tract and perceptual speed. For **Study II**, we expanded the model by including a LCM on leisure activity engagement. Based on ratings from an independent sample of participants aged 78 years and older from a later wave of SNAC-K, we clustered the activities with respect to their rated intellectual, physical and social component. The cluster analysis resulted in 4 clusters of activities which we labelled "predominantly social", "complex", "predominantly physical", and "low-level", based on their respective profile of intellectual, physical, and social involvement. For each of the clusters, we defined an LCM by directly specifying a change score as the difference between the 2 observed scores (one at each occasion). We ran a trivariate LCM with each of four activity clusters and each of the two white matter measures (FA and MD) in CS tract.

4.2.3 Results

Frequency of leisure activity engagement declined on average in all clusters, with significant variability among individuals in the rate of change. We first tested whether these inter-individual differences in change were correlated with inter-individual differences in change in perceptual speed. Such a link was observed for the cluster of "predominantly social" activities (r = .19, χ^2 = 4.54, p = 0.03), but not for the other clusters (r's = |.23|, χ^2 < 2.65, p's > 0.10). The cluster of "predominantly social" activities consisted of going to a restaurant, bar or café; attending theatre, cinema, or concert; volunteering; church service; playing chess or cards. Change in frequency of engagement in the same "predominantly social" cluster was related to change in FA (r = .62, χ^2 = 8.0, p = 0.005) and MD (r = -.56, χ^2 = 7.23, p = 0.007) in the CS tract.

To test whether change in white matter microstructure statistically mediates the association between change in "predominantly social" activities, we defined directed regression paths instead of covariances between the change scores. The indirect effect via white matter microstructure was significantly different from zero according to the unstandardized bias-corrected bootstrapped confidence intervals (FA: unstandardized indirect effect = .337; 95% CI: .039, 3.408; standardized

indirect effect = .598; MD: unstandardized indirect effect = .305, 95% CI: .005, 1.553; standardized indirect effect = .556). The direct effect of change in engagement in "predominantly social" activities was no longer significant when white matter measures were introduced in the model (model with FA: unstandardized direct effect = -.227, χ^2 = 2.34, p = 0.13; standardized direct effect = -.403; model with MD: unstandardized direct effect: -.202, χ^2 = 2.07, p = .15; standardized direct effect = -.364).

4.2.4 Conclusion

Changes in white matter microstructure are an important structural correlate of perceptual speed that may play a role in explaining the association between changes in social activities and perceptual speed in individuals older than 80 years. The role of white matter microstructure in old-age cognition seems not specific to ages above 80 years (Bender et al., 2016; S. J. Ritchie et al., 2015), but we speculate that predominantly social activities might be especially important in very old age, as physical ability gets at its limits for many persons in this age segment, limiting the opportunities for engagement in activities with a stronger physical component. In short, differences between people in how often they leave the house and meet other people is related to differences in white matter microstructure and perceptual speed.

4.3 STUDY III: PHYSICAL ACTIVITIY, DOPAMINE $D_{2/3}$ RECEPTOR AVAILABILITY AND COGNITIVE PERFORMANCE

4.3.1 Background

As noted, between-person differences in cognitive performance in older age are associated with differences in physical activity (Bauman et al., 2016; Blondell et al., 2014; Boraxbekk et al., 2016; Memel et al., 2016; Prakash et al., 2015; Sofi et al., 2011; Willey et al., 2016). The neurotransmitter DA is involved in cognitive functions such as episodic memory (Bäckman et al., 2011; Bäckman et al., 2010; Bäckman et al., 2006; Cervenka et al., 2008; Lisman et al., 2011; Nyberg et al., 2016; Shohamy & Adcock, 2010) and working memory (Cools & D'Esposito, 2011; Liggins, 2009; Takahashi, 2013; Takahashi et al., 2008) and the DA system deteriorates with advancing age. Animal data (Lin & Kuo, 2013) and one study on human patients (Robertson et al., 2016) suggest that physical activity modulates DA receptor availability. Epidemiological studies suggest a protective effect of physical

activity on risk of PD (Xu et al., 2010; Chen, et al., 2005; Thacker et al., 2008). However, data from healthy humans on associations between habitual physical activity and dopamine functioning are lacking so far.

4.3.2 Method

4.3.2.1 Participants

We analyzed data from 178 participants of the COBRA study, all around retirement age (*M* = 66.14 years, *SD* = 1.21; education: *M* = 13.29 years; *SD* = 3.51; female: 44.7 %).

4.3.2.2 Materials and data analyses

Engagement in physical activity was analyzed both with respect to self-reported frequency (hours /week) and intensity. Participants indicated for how many hours per week they had engaged in walking bicycling, jogging, gym training, and sports. We aggregated the hours/ week for each participant by summing up across activities. In addition to how often each activity was performed, it was asked how physically demanding it would normally be to perform the activity in question (on a scale from 1 = "not at all" to 5 = "extremely"). Using SEM, we formed a latent factor of the activities' intensity (or "demandingness") for each person, across the 5 activities. We counted only ratings for activities that a given person also had indicated to engage in for at least 1 h /week, so that the latent intensity factor should represent a person's tendency to rate her/ his frequent physical activities as demanding (that is, the activities he or she does on a daily to weekly basis). To assess $D_{2/3}$DR availability, BP_{ND} was calculated for the ROIs caudate, putamen, and hippocampus, with cerebellum as reference region. The common variance across the left and right hemisphere of each structure was modeled as a latent factor for that hemisphere and included in the same SEM. Of the cognitive tests in COBRA, we used 3 tests (one verbal, one numerical, and one spatial) in each of the domains episodic memory, working memory, and processing speed. Using SEM, we formed a latent factor for cognitive ability in each domain.

We defined a SEM that combined all variables for physical activity (observed frequency, latent factor for intensity), BP_{ND} (latent factors for putamen, caudate and hippocampus), and cognitive performance (latent factors for episodic memory, working memory, and speed). The covariances among all latent variables and of the latent variables with physical activity frequency were estimated. Age, education, and sex were included as

covariates in the SEM to statistically control for variance related to these factors when examining the inter-relationships between the variables of interest.

4.3.3 Results

We observed a correlative triad between the latent factor for intensity of physical activity, episodic memory, and $D_{2/3}$DR BP_{ND} in the caudate nucleus. Intensity of physical activities was positively correlated to $D_{2/3}$DR BP_{ND} in caudate ($r = .32$; $\Delta\chi2 = 14.49$; $df = 1$; $p < .001$) and with episodic memory ($r = .30$; $\Delta\chi2 = 11.08$; $df = 1$; $p < .001$; Fig. 2b). As reported previously (Nyberg et al., 2016), episodic memory was correlated with D2/3DR BPND in caudate ($r = .20$; $\Delta\chi2 = 4.69$; $df = 1$; $p = .03$). Apart from this triangle, intensity of physical activity was also positively associated with working memory ($r = .43$; $\Delta\chi2 = 19.23$; $df = 1$; $p < .001$), but not with perceptual speed ($r = –.01$; $\Delta\chi2 = .007$; $df = 1$; $p = .93$), and not with $D_{2/3}$DR BP_{ND} in putamen ($r = .16$; $\Delta\chi2 = 3.11$; $df = 1$; $p = .08$) and hippocampus ($r = –.02$; $\Delta\chi2 = 0.06$; $df = 1$; $p = .80$).

Frequency of physical activity was unrelated to episodic memory, working memory, and speed, as well as to D2/3DR BPND ($rs < |.10|$; $\Delta\chi2 < 1.53$; $ps > .22$). Expectedly, the three cognitive abilities were related to one another (all $rs > .23$; $ps < .01$), as was D2/3DR BPND in the three ROIs (all $rs > .30$; $ps < .001$). Frequency of physical activities was unrelated to the intensity factor ($r = –.05$; $\Delta\chi2 = 0.39$; $df = 1$; $p = .53$).

4.3.4 Conclusion

We observed that subjective intensity of physical activity was related to $D_{2/3}$DR availability in caudate and to episodic memory performance, which in turn was related to $D_{2/3}$DR availability in the same region. Considering the extant literature, we conclude that the density of $D_{2/3}$DR in caudate is a potentially important player in accounting for the influence of physical activity on episodic memory, or that $D_{2/3}$DR availability in caudate is involved in motivation to engage in physical activity, which might in turn benefit cognition. Both causal pathways seem plausible and are not mutually exclusive.

4.4 STUDY IV: RELATIVE IMPORTANCE OF PREDICTORS OF CHANGES IN PERCEPTUAL SPEED

4.4.1 Background

Cognitive ability in old age is related to a host of factors, including common genetic variation (Reynolds, Gatz, Berg, & Pedersen, 2007; Tucker-Drob, Reynolds, Finkel, & Pedersen, 2014), early life influences such as education (Lenehan, Summers, Saunders, Summers, & Vickers, 2015), personality traits (Curtis, Windsor, & Soubelet, 2015), physical health and fitness (Demnitz et al., 2016; Nash & Fillit, 2006), as well as lifestyle factors such as physical activity (Blondell et al., 2014; Sofi et al., 2011) and other types of leisure activity engagement (Ghisletta et al., 2006; H.-X. Wang et al., 2013; see also Study II). Some of these factors have been predictive of subsequent change in cognitive performance, but previous studies that combined a larger number of predictors to assess their combined predictive strength were not able to explain much of the variance in change in cognition (Albert et al., 1995; S. J. Ritchie et al., 2016). With regard to leisure activity engagement, the strength of associations with cognitive performance that we observed in **Studies II** and **III** was not impressive, raising the question how important leisure activities really are in predicting cognitive change, compared to other lifestyle- and health-related factors. A major challenge in investigating the predictive power of these factors is that they may interact in ways difficult to pre-specify. Here we took an exploratory approach, SEM trees and SEM forests (Brandmaier et al., 2016; Brandmaier et al., 2013), to estimate the relative importance of each predictor variable in a large set of commonly considered predictors of cognitive decline. We derived variable importance, a measure that subsumes the direct effect of a predictor and all interactions with the other predictors. Here we focused on perceptual speed as a measure of cognitive ability, because it has been shown to be an indicator of aging-related decline in fluid cognitive abilities (Finkel et al., 2007; Lindenberger et al., 1993; Salthouse, 1996, 2000).

4.4.2 Method

4.4.2.1 Participants

We included data from 1,046 participants from the baseline assessment in SNAC-K, and 6-year follow-up data from 760 of them. All participants were cognitively healthy at baseline and 6-year follow-up. This effective sample

included only persons for whom data on all predictors and on perceptual speed at baseline were available.

4.4.2.2 Measures and data analyses

Using SEM, we defined a latent factor of perceptual speed with performance on digit cancellation and pattern comparison as indicators. We estimated 6-year change in perceptual speed using a LCM.

As predictors of change in perceptual speed, we included baseline measures of age, sex, educational attainment, retirement status, *ApoE* status, frequency of leisure activities of various types, frequency of social interaction, social network size, smoking, BMI, hypertension, diabetes, cholesterol levels, walking speed, number of chronic conditions, and the personality traits extraversion, neuroticism, and openness. We used these predictors in a SEM forest to assess their relative importance and in a single SEM tree for an illustrative example of a pattern of conditional effects of the predictors on change in perceptual speed. We defined mean change in perceptual speed as the focus parameter in all analyses.

4.4.3 Results

The SEM forests indicated that age, retirement status, multimorbidity and walking speed play a major role in explaining between-person differences in change in perceptual speed, in interaction with each other and with other predictors such as leisure activities, educational attainment, and personality. In comparison, *ApoE*, hypertension, cholesterol, and current smoking were non-informative in this analysis. Social interaction, social network size, and social activities, as well as extraversion, diabetes, physical activity, sex, neuroticism, and BMI were somewhat predictive of change in perceptual speed, but with relatively low importance. Partial dependence plots indicated also that the largest difference between age groups in change in perceptual speed is between 60 (less decline) and 66 (more decline), and then again between 66 and 72 (even more decline). After that, the differences level out (similar rate of decline). About the same difference is seen in the partial dependence comparing non-retired to retired persons, suggesting that the similarly high importance of age and retirement status represents the same effect. Walking speed had a flat partial dependence in perceptual speed change, suggesting that its importance stems from interactions only. Another technical possibility is that it reflects direct effects on other parameters in the model, such as mean perceptual speed performance at baseline, which may

have covaried with change in perceptual speed in certain constellations. Partial dependence plots for multimorbidity indicated small negative effects such that more diseases were associated with steeper decline, when the effect of other variables was averaged out.

4.4.4 Conclusion

To conclude, age, retirement, walking speed and multimorbidity were the most important predictors of subsequent change in perceptual speed, followed by intellectual-solitary, intellectual-social, and complex leisure activities. The predictive power as reflected in the importance measures of these variables are likely partly determined by complex interactions with one another and with further predictors entered into the analysis. We conclude that important information about imminent cognitive decline can be found in complex interactions among commonly considered predictors. Our results can be seen as a starting point in understanding non-linear and interactive effects on cognitive change, which are to be confirmed in future studies.

5 DISCUSSION

5.1 AIM A) IDENTIFY LIFESTYLE COMPONENTS THAT ARE RELATED TO LATE-LIFE COGNITIVE PERFORMANCE

Studies II-IV in this thesis contributed to identifying components of lifestyle that are related to late-life cognitive performance, which was the first aim of this thesis. In **Study II**, we found that in a sample of individuals older than 80 years, 3-year changes in predominantly social activities were related to differences in change in cognitive performance (indicated by perceptual speed). In other words, persons over 80 years that maintained their level of engagement more than others also maintained their level of perceptual speed performance better than others. This association was evident only for predominantly social activities, which was an activity category that required leaving home and involved some level of social interaction: visiting a restaurant, pub, or café; attending the theatre, cinema or concert; volunteering; church service; playing chess or cards. We assigned the label "predominantly social" because these activities were rated as containing a social, limited mental and physical component. Previous studies of change in social activities and performance in different cognitive domains have yielded mixed results (Bielak, Cherbuin, Bunce, & Anstey, 2014; Bielak et al., 2007; C. L. Brown et al., 2012). Based on data from 4 longitudinal studies, Brown et al. (2012) reported associations between change in social activities and change in verbal fluency. Changes in reasoning and episodic memory were associated with changes in social activities in 3 of the 4 studies. Perceptual speed was not included in these analyses. Bielak et al. (2014) found that change in cognitive activities, but not in social or physical activities, was related to change in perceptual speed. Thus, our results match previous findings only as far as one can generalize across different cognitive domains or activity types. Part of the explanation for the association between social activities and perceptual speed may be the cognitively stimulating effect of social interactions (Windsor et al., 2014; Ybarra et al., 2008) related to meeting other people regularly. It could also reflect the social support that other persons involved in the activities might offer (Ellwardt, Aartsen, Deeg, & Steverink, 2013; T. E. Seeman, Lusignolo, Albert, & Berkman, 2001; Zahodne, Nowinski, Gershon, & Manly, 2014). In addition, almost all of these activities require some physical activity, include cognitive tasks with demands on navigating, and other sources of cognitive stimulation through interaction with the physical environment. The involvement with the

socio-cultural environment that these activities imply may also contribute to a sense of belonging. Note that the mean frequency of engaging in these activities was not high to begin with, so that "occasional participation in socio-cultural activities" is a more precise description of what differed between the more active and the less active participants in **Study II**. However, as our data are not informative regarding causal directionality, we might observe this association because participation in these activities is a marker of general health and those participants over 80 years who decrease their activity level may be doing so because of health problems. Such problems can both lead to and result from decreased activity engagement. In either case, they may affect perceptual speed performance negatively. Both this third-variable effect and a direct effect of activity participation on perceptual speed seem plausible in the light of the extant literature, and, as they are not mutually exclusive, both could account for part of the association found.

In **Study III**, we investigated associations between physical activity and cognitive performance. Within the physical activity domain, we measure self-reported frequency of engagement and self-rated demandingness of the activities the participants engage in. We estimated the participants' tendency to rate their physical activities as demanding for walking, bicycling, jogging, gym training, and sports, only counting those activities that a given participant pursued at least 1 h/week. Thus, the tendency to rate activities as demanding refers only to rather frequently pursued activities. Note that this tendency was unrelated to the overall frequency of engagement. We would like to stress that the tendency to rate the pursued activities is an entirely subjective measure that can be different for persons who engage in exactly the same activities equally often. Thus, we conceive of this measure as a proxy for the subjective intensity of engaging in these activities. This latent "intensity" factor was associated with working memory and episodic memory, but not perceptual speed.

Physical activity is the most studied type of leisure activity when it comes to effects on health and cognitive performance, and most studies focused on frequency or frequency and intensity combined, many of them reporting positive associations with cognitive performance (Ahlskog et al., 2011; Bauman et al., 2011; Blondell et al., 2014; Prakash et al., 2015; Sofi et al., 2011). However, a frequency-independent measure of intensity of physical activity was positively related to cognition in two cross-sectional (Angevaren et al., 2007; B. M. Brown et al., 2012), and two longitudinal (Angevaren et al., 2010, van Gelder et al., 2004) studies. We did not observe any effects of frequency of physical

activity on cognitive performance, which was unexpected. This could be due to the overall high frequency of activity in the study population. For instance, 87,7 % of the participants cycled at least 1hr/week.

In this population, between-person differences in intensity, rather than frequency, seem to bear information related to cognitive performance. That is, it is not whether or not, but rather the way in which people are physically active that matters. Participants' tendency to rate their regular activities as demanding, as reflected in the latent "intensity" factor, is an inherently subjective measure, reflecting characteristics more of persons than of activities. Few observational studies have focused on intensity of physical activity (Angevaren et al., 2010; Angevaren et al., 2007; B. M. Brown et al., 2012; van Gelder et al., 2004). Data from exercise interventions seem to be inconclusive as to whether intensity of aerobic exercise benefits cognitive performance (P. J. Smith et al., 2010), and even the effect of aerobic exercise interventions *per se* is not unequivocal (Prakash et al., 2015; Young et al., 2015). To our knowledge, no study has related participants' tendency to rate their activities as demanding to cognitive performance. A person's tendency to experience his or her physical activity as demanding might reflect a habitual level of vigor of engaging in the activity. Conceivably, this tendency is habitual, trait-like, and rather stable, because participants were asked how demanding the activity normally would be for them. However, longitudinal assessments are still needed to show whether this assumption holds true. If it reflects vigor of engagement, the tendency to experience the pursued physical activities as demanding might be related to motivation. In conclusion, inter-individual differences in the intensity of engaging in frequent physical activities are partly linked to inter-individual differences in working memory and episodic memory performance.

The associations between leisure activities and cognitive performance observed in **Studies II** and **III** were of modest strength, and we speculated that effects of engagement in leisure activities or physical activity might be contingent on other factors that shape the opportunities for and efficiency of lifestyle choices. In **Study IV**, we applied an exploratory method to learn more about the relative importance of leisure activities and other health-related factors, in predicting 6-year change in perceptual speed. This method takes the potential mutually interactive effects of predictor variables into account. We used four clusters of leisure activities as predictors, along with age, physical health and fitness indicators, personality, education, retirement status and *ApoE* status. After age and physical-health related variables, engagement in

all groups of leisure activities were of relatively high importance for predicting subsequent change in perceptual speed. Physical activity, however, was relatively less important in this analysis, which was unexpected. The physical activity measure we used was a combination of frequency of engagement and type of activity (pre-defined moderate or vigorous intensity type of activity) based on WHO-recommendations for insufficient, health-enhancing, and fitness-enhancing activity (Rydwik et al., 2012) and was related to perceptual speed at baseline in SNAC-K (Ferencz et al., 2014). It is difficult to interpret this null finding, and it remains to be determined whether it reflects the way of defining physical activity level or whether physical activity is really so much less related to subsequent change in perceptual speed than other types of leisure activities.

Collectively, the results from **Studies II-IV** suggest that between-person differences in leisure activity engagement are related to differences in cognitive performance. Direct comparisons among the studies are limited by differences in type of leisure activity engagement, study sample, study design, and cognitive measures used. The perhaps most important difference among **Studies II-IV** concerns the type of leisure activity, with **Studies II** and **IV** focusing on clusters of leisure activities based on ratings of intellectual, social and physical components. In **Study II**, we found change-change associations of perceptual speed only with a predominantly social cluster, but level-level associations with all activity clusters. In **Study IV,** we focused on whether level of activity could predict change in perceptual speed and observed almost similar predictive utility for all clusters. In **Study III** and **IV**, we used measures of physical activity. In **Study III**, we separated frequency from subjective intensity and observed associations with subjective intensity only. In **Study IV**, we used a combined frequency and intensity measure with three categories based on recommendations by the WHO, which seemed rather weakly predictive of change in perceptual speed.

Differences in the age range of the study samples should be noted. **Study II** included only persons older than 80 years, because longitudinal data on white matter microstructure was available only for this age segment. We found predominantly social activities, but not physical, complex, or low-level activities to show change-change associations with perceptual speed. In **Study III**, participants were sampled from a narrow age range around retirement age, and in this rather healthy and physically active group, intensity of physical activity was related to cognitive performance, which is in accordance with studies on young-old persons (Angevaren et al., 2010; Angevaren et al., 2007; B. M. Brown et al.,

2012). However, many other studies with participants in this age range also found associations between frequency of physical activity and cognitive performance (Bauman et al., 2016; Blondell et al., 2014; Boraxbekk et al., 2016; Memel et al., 2016; Prakash et al., 2015; Sofi et al., 2011; Willey et al., 2016). One possibility is that our participants might have been so active overall that differences in frequency were all within the range of sufficient activity. In **Study IV**, a large proportion of participants was between 60 and 70 years, but there were also older persons. As age was the predictor with the highest importance, it is likely that the predictive effect of other variables interacted with age, that is, patterns of predictors might have been conditional upon the age of the participants in the SEM forest. In addition, the different cognitive domains we focused on makes the studies difficult to compare. In **Studies II and IV,** we focused on perceptual speed change as an indicator of change in fluid general ability (Ghisletta et al., 2003; Finkel et al., 2007). In **Study III**, we examined episodic memory, working memory, and perceptual speed.

To summarize, we identified components of leisure activities that were related to cognitive performance and change therein. In individuals older than 80 years, change in occasional involvement with the socio-cultural environment went along with change in perceptual speed (**Study II**). In individuals between 60 and 100 years of age, baseline level of engagement in all kinds of leisure activities was predictive of subsequent 6-year change in perceptual speed (**Study IV**). In persons around retirement age, intensity of engagement in physical activity was related to performance in episodic memory and working memory (**Study III**).

5.2 AIM B) IDENTIFY BRAIN CORRELATES OF LIFESTYLE AND COGNITIVE PERFORMANCE IN LATE LIFE

In **Studies I and II**, we were interested in white matter microstructure as a structural brain characteristic that changes in aging, where changes might relate to aging-related cognitive decline as well as to changes in leisure activity engagement. With **Study I**, we were among the first to observe change-change associations between white matter microstructure and perceptual speed as an indicator of general cognition (Bender et al., 2016; Charlton, Barrick, Markus, & Morris, 2013; Charlton et al., 2010; S. J. Ritchie et al., 2015). Such an association was expected based on previously established cross-sectional associations between white matter microstructure and perceptual speed (Laukka, Lövdén, Kalpouzos, et al., 2013; Penke et al., 2012), and is biologically plausible

as white matter microstructure is thought to reflect myelination of neuronal fiber bundles that constitute the large tracts of white matter (Fields, 2008). White matter tracts connect brain areas and their myelination is directly related to the speed with which information is transferred.

In **Study II,** we aimed at identifying leisure activities in which change is associated to both change in white matter microstructure and perceptual speed, and found this to be the case with a cluster of activities that are characterized by involvement with the socio-cultural environment. The association between engagement in these activities and white matter microstructure can reflect a beneficial effect of activity engagement on white matter microstructure. Staying involved with the socio-cultural environment might pose demands on the neuro-cognitive system that might require brain maintenance (Nyberg et al., 2012), or even plasticity, if sufficiently demanding (Lövdén, Bäckman, et al., 2010). White matter microstructure is malleable and sensitive to experience well into late life (Lövdén, Bodammer, et al., 2010). It is therefore plausible that inter-individual differences in maintenance of white matter microstructure underlie the association between activity engagement and perceptual speed. The mediation model suggested an indirect effect of change in leisure activities, which indicates that all variance that is shared by change in activity engagement and perceptual speed is also shared with white matter microstructure. In other words, persons who change in both leisure engagement and perceptual speed do also change in white matter microstructure in the corticospinal tract. This result is compatible with the biologically plausible hypothesis that white matter microstructure is an important neural underpinning of perceptual speed that is also associated with leisure activity engagement.

As a neurochemical correlate of both leisure activity engagement and cognition, we focused on indicators of DA signaling in **Study III.** We identified self-rated intensity in engaging in physical activities to correlate with dopamine $D_{2/3}$ receptor availability in caudate nucleus and as well as with episodic memory. To our knowledge, we are the first to observe an association between physical activity and dopamine receptors in healthy humans. To discuss the biological plausibility of this association, we reviewed animal and patient studies. There are several pathways that could explain the association between physical activity intensity and $D_{2/3}$DR availability, including both directions of causal influence: More activity enhancing $D_{2/3}$DR, and more $D_{2/3}$DR resulting in more spontaneous activity. Toward this end, animal studies have documented that exercise leads to increased expression of $D_{2/3}$DR (e.g. Fisher et al., 2004;

Vuckovic et al., 2010) down-regulation of DA transporter proteins (Fisher et al., 2004; Petzinger et al., 2007), expression of mitochondrial biogenesis and enzymatic antioxidant defenses (Aguiar et al., 2016), and increasing dendritic spine density and arborization (Toy et al., 2014, for review see Petzinger et al., 2013). All these mechanisms lead to alleviation or reversal of the effects of experimentally induced DA deficiency. Others have suggested a pathway by which exercise results in enhanced DA synthesis via changing calcium levels in the blood (Sutoo & Akiyama, 2003). On the other hand, persons with greater DA-system integrity might be more prone to engage in physical activity. Mice given a $D_{2/3}$DR antagonist lose their natural preference of wheel-running over sucrose consumption (Correa et al., 2016). D_2DR knockdown mice fed with obesity-inducing diet and placed in an enriched environment engaged less in voluntary exercise, spent less energy, and gained more weight than their wild-type counterparts with the same diet and environment (Beeler, Faust, Turkson, Ye, & Zhuang, 2016). This suggests that the ability to express D_2DR enabled the wild-type mice to take advantage of the enriched environment by engaging in physical activity. In humans, a polymorphism in the $D_{2/3}$DR gene has been related to levels of habitual physical activity in women (Simonen et al., 2003), suggesting that genetically determined individual differences in $D_{2/3}$DR expression might result in differences in physical activity engagement.

In summary, we identified microstructural white matter changes as a brain correlate of changes in leisure activity engagement and cognitive performance in late life. Further, we documented $D_{2/3}$DR availability as a brain functional correlate of level of physical activity intensity and performance in episodic memory and working memory.

5.3 AIM C) EXPLORE THE RELATIVE IMPORTANCE OF LIFESTYLE AND HEALTH-RELATED FACTORS IN COGNITIVE AGING

In **Study IV**, we conducted an exploratory data analysis based on SEM trees and forests to predict inter-individual differences in change in perceptual speed and to estimate the relative importance of different predictors of change in perceptual speed. SEM forests allow for computing an importance measure for each predictor, which subsumes the unconditional effect of the variable and the effects of the variable conditioned upon, or in interaction with, any other variable in the SEM forest. The SEM forests indicated that age, retirement status and walking speed play a major role in predicting between-person differences in change in perceptual speed, followed by number of chronic diseases, leisure activities,

educational attainment, and personality. The partial dependence plots for leisure activities indicated no marginal effect of leisure activity variables after averaging out effects of the other variables. This suggests that a most of their importance probably emanated from effects conditioned upon other variables such as age, retirement status, and physical health and functioning. Leisure activities, therefore, seem to be important predictors of decline in perceptual speed, but their predictive value might depend on how old and healthy a person is. How much of the variable importance is due to conditional effects, and how much to direct effects remains to be determined.

5.4 LIMITATIONS

There are limitations to the data and methods to consider when interpreting the results obtained in this thesis. These include the validity of the measurements, how the observational nature of the study designs and the inter-individual differences approach precludes certain interpretations of the result, and how characteristics of the study participants limit generalizing the conclusions to the general population.

5.4.1 Validity of the measurements

5.4.1.1 Activity questionnaires

Self-reported data are subject to validity threats such as biased recollection and social desirability, adding noise or undesired variability to the data. Objective measures such as mobile activity monitors to measure physical activity (Sasaki, John, & Freedson, 2011) and measures that require less retrieval from long-term memory, such as questions about activities of the previous day (Lövdén et al., 2005; Moss & Lawton, 1982) could complement questionnaire data. However, note that in **Study III**, we deliberately made use of a subjective measure of physical activity intensity and learned that it contained interesting information about inter-individual differences that we interpreted as being an individual's tendency to exert vigor and effort into the physical activities performed. However, this measure needs to be further validated in other samples. By using measures of subjective experience in **Study II** and **III** we contributed to the breadth of measurements used in the field (Fallahpour et al., 2016).

The frequency scale in **Study III** could have induced a frame of reference that resulted in overreporting of physical activities. The question was phrased: "How many hours per week do you… " (in a normal summer week),

and the scale for answering comprised of integers from 0 to 14, followed by 15+. One problem that could have led to overreporting is that there was no option to report activities engaged in less than 1 hr/week, but still regularly. Another problem is the frame of reference induced by the scale (Schwarz, Bless, Bohner, Harlacher, & Kellenbenz, 1991; Schwarz, Grayson, & Knäuper, 1998; Schwarz & Hippler, 1994). Participants might have gotten the impression that 0 is "little", 7-8 is "normal" and 15+ is "a lot". This might explain, at least in part, the high activity frequency in Study III's participants, and might have added unrelated variance to the measure making it more difficult to detect associations with any other variable (as a reminder: physical activity frequency was not associated to any other variable in **Study III**).

5.4.1.2 Brain measurements

With regard to the white matter microstructure measures used in **Studies I** and **II**, we note that due to the fact that SNAC-K started in 2001, the DTI measurements do not meet today's standards. FA and MD from DTI are measures of water diffusion in the brain at the level of a voxel. The relatively low spatial resolution of the DTI data precludes detection of small fiber bundles and comes with the possibility of partial volume effects that could not be accounted for by TBSS processing. Moreover, if fibers within a voxel go in different directions while crossing, kissing, merging or fanning, the mean FA value for the voxel is not informative of the microstructure (Jeurissen, Leemans, Tournier, Jones, & Sijbers, 2013). We tried to minimize these problems and take a conservative approach by restricting the use ROIs to the core skeleton of the largest white matter tracts. Further, by using SEM we eliminated hemisphere-specific variance that might partly reflect random noise and partly meaningful variance not of interest for this study.

With respect to the measures of $D_{2/3}$DR availability in **Study III,** PET imaging with the radioligand [^{11}C]raclopride is a well-established quantification of D2DR availability in striatum. In hippocampus, where D2DR are much less abundant, it has been less often used to measure D2DR availability. We found the hippocampal BP values to be lower than in striatum, but positive and reliably higher than in the cerebellum reference region (Hall et al., 1994; Nyberg et al., 2016). A caution to keep in mind is that [^{11}C]raclopride can be displaced by endogenous DA at its target receptors (Ginovart, 2005; Ross & Jackson, 1989; P. Seeman, Guan, & Niznik, 1989). Consequently, binding

potential, or $D_{2/3}$DR availability, not only reflects receptor density and affinity, but is also affected by endogenous DA levels.

5.4.1.3 Cognitive tests

The cognitive test battery in SNAC-K was designed for a longitudinal study to assess risk- and protective factors and early markers for cognitive decline and dementia. It is therefore not exhaustive and all-encompassing with respect to psychometric models of human cognitive abilities. However, the baseline measurements of perceptual speed, episodic memory, semantic memory, letter fluency and category fluency that we used here was fitted to a SEM representing correlated latent ability factors with two indicator tasks each. These factors represented the cross-sectional variance-covariance structure well (Laukka et al., 2013) and validated our approach to use latent variables in **Studies I**, **II**, and **IV**. A possible limitation of the perceptual speed data is that they largely rely on rapid fine-motor actions (motor speed), since it is paper-pencil based.

The cognitive test battery in COBRA is completely computerized and has been validated in another large-scale intervention study, the COGITO study (Schmiedek et al., 2010). A particular strength of this battery is that it includes three tasks within each cognitive domain to allow for robust estimation of measurement models using SEM. Moreover, the three tasks are designed so that they contain verbal, numerical, and spatial/ figural material each, which should result in latent factors that generalize across stimulus materials.

5.4.2 Causal inference

All studies in this thesis are observational; no experimental manipulation or intervention was conducted. The observed associations can therefore not be interpreted in causal terms. Still, the studies differ in how informative they are of the processes of interest. When longitudinal, the data bear information about within-person changes in the aging process. **Study II** is perhaps most informative regarding associations between leisure activities and cognitive aging, as change in leisure activity relates to what actually shapes an individual's lifestyle in the period of interest, namely very old age (> 80 years). Whether a person stays active or drops some activities during a certain time period may tell more about his or her aging trajectory than a snapshot measurement. Still, the associations could be due to third variables causing change in white matter microstructure, change in leisure activity engagement, and change in perceptual speed (e.g. impending dementia or other pathological changes). We tried to

minimize such effects by excluding participants with a dementia diagnosis at time 1 or follow up and by statistically controlling for change in white matter lesions. White matter lesions seem to play a role in the association between leisure activity engagement and white matter microstructure, as including change in white matter lesions statistically accounted for some of the association. This finding is in line with the view that an active lifestyle protects against white matter lesions (Booth et al., 2014; Hafsteinsdottir et al., 2012), which in turn are related to white matter microstructure (Vernooij et al., 2009).

When using a cross-sectional measure of leisure activity engagement as a predictor of subsequent cognitive decline, as we did in **Study IV** for other methodological reasons, what we are measuring with time 1 engagement represents a mix of previous level and changes that we cannot disentangle. For example, a person with a low engagement level at time 1 might have had a rather low level throughout the lifespan, or might have just changed from a higher or lower level. Theoretically, we would expect that the actual level is less telling without any information about changes, as many possible trajectories could have led to this level (Lindenberger et al., 2011). However, at least when it comes to the leisure activity measurements in COBRA and SNAC-K, participants are asked to report activities engaged in within the last 12 months. Thus, the cross-sectional snapshot was obtained from a 1-year period, which should have "blurred out" shorter-term variations within individuals. Still, cross-sectional data represent a mix of level and change information and are therefore difficult to interpret when it comes to associations with change. In spite of this, a design that includes time 1 measures of lifestyle characteristics as predictors of cognitive change is the most widely used design in observational studies in this field, an advantage being that associations between level in measure 1 and change in measure 2 suggest a dynamic influence between measures. However, a reverse direction of causal influence is not precluded in such a pattern of results. Studies that report associations between previous cognitive ability and later leisure activity (Gow, Corley, Starr, & Deary, 2012; Gow, Mortensen, & Avlund, 2012; Saczynski et al., 2006) challenge common conclusions about causal directionality drawn from such studies and point at possible "reverse causation", with cognitive ability affecting inter-individual differences in engagement rather than the other way around. Using data from the Lothian Birth Cohort, Gow et al. (2012) observed that the cross-sectional association between leisure activities and cognitive abilities at age 70 was fully explained by intelligence at age 11 (see also Gow, Mortensen, et al., 2012). Thus, the directions of dynamic (or

longitudinal) associations remain to be determined. To exclude reverse causation, many authors of longitudinal studies control for baseline cognition and education when determining associations between engagement at baseline and change in cognition. This ensures that the remaining effects of engagement on cognitive change are statistically independent of these markers of previous cognitive abilities. However, to simultaneously test both hypotheses, a study would need a follow-up period long enough to allow for aging-related changes in both engagement and cognition to take place, several repeated measurements of both variables, and analytic tools to integrate both directions of influence in the same statistical model (see 1.3.4.3). In the **Studies I-III**, the directionality of causal influence could not be determined based on the nature of the data. **Studies I** and **II** are based on two measurement occasions, and we focus on change-change associations which should be most informative of aging-related change. In **Study IV**, we use baseline data of many variables to predict change in perceptual speed. As we are not investigating the effect of level of perceptual speed on change in the predictor variables, reverse causation cannot be excluded.

Note that all analyses of covariance structures from inter-individual differences have only limited bearing on intra-individual covariance structures (Kievit, Frankenhuis, Waldorp, & Borsboom, 2013; Schmiedek, Lövdén, von Oertzen, & Lindenberger, 2016). The data being ultimately correlational, Simpson's paradox can occur and an association that is negative between individuals may be positive within individuals, as illustrated by the following example: "It may be universally true that drinking coffee increases one's level of neuroticism; then it may still be the case that people who drink more coffee are less neurotic" (Borsboom, Kievit, Cervone, & Hood, 2009, p. 72). Applied to the mediation analysis in **Study II**, this means that from the fact that persons who change in leisure activity engagement and perceptual speed do also change in white matter microstructure, it cannot be derived that more leisure activity engagement is linked to faster speed and better white matter microstructure within an individual. That is, the results of the mediation analysis should be interpreted at the between-person level.

Note also that the SEM tree approach taken in **Study IV** does not imply any hierarchy among the predictors, such that genes influence endophenotypes, which in turn influence behavior. Instead, SEM trees and forests are treating predictors equally to start with and evaluate their predictive utility (Brandmaier et al., 2016; Brandmaier et al., 2013). SEM can be used to formalize models that are theoretically based on a hierarchy of influencing

factors from genes via endophenotypes to behavior, as in a recently proposed watershed model (Kievit et al., 2016). On a related note, SEM trees and forests can be seen as a method to *predict* differences in any given outcome (formally defined in a SEM), which is conceptually different from *explaining* variance (Breiman, 2003; Shmueli, 2010).

5.4.3 Generalizability

Data from both SNAC-K and COBRA are limited in their generalizability to the populations. SNAC-K participants (**Studies I**, **II**, and **IV**) live in a well-off area in central Stockholm. For example, financial hardship was rare (< 10%) in the effective sample of **Study IV**. Thus, this variable or related information on socio-economic situation was not included in the analysis although it would have been of theoretical interest.

In COBRA, participants from rural areas were included, but the effective sample had an unusually large share of persons with high education, with 44% of the participants having undergone more than 13 years of formal schooling.

5.5 CONCLUSIONS

In the course of this doctoral work, my coauthors and I have identified different types of leisure activities to be related to level and change of cognitive performance, in level and in change. Among older adults in their mid-60s, self-rated intensity in physical activity was related to cognitive performance. For the first time in healthy humans, we documented DA D2 receptor availability as a neural correlate of physical activity intensity. In older adults (81+ years), changes in occasional participation in socio-cultural activities were related to changes in perceptual speed. We identified changes in white matter microstructure as a neural correlate of these changes in activities and speed. As the direct associations between leisure activity and cognition were modest in these studies, we conducted an exploratory analysis using a data-mining technique to investigate the relative importance of leisure activity engagement as a predictor of change in cognition. We conclude from the results of this exploratory study that level of leisure activity engagement is indeed an important predictor variable of change in perceptual speed (as indicator of cognitive aging), and that its importance probably partly depends on constellations of age- and health-related factors.

5.6 OUTLOOK

We reiterate what others identified as steps forward in the field, and add lessons learned specifically from the studies in this thesis. First of all, there is a need for more longitudinal studies in cognitive aging research that include brain correlates. **Studies I** and **II**, both on change-change associations, are those with the most use of longitudinal data. Yet, with two measurement occasions, all changes measured had inevitably to occur in parallel. Longitudinal studies with three or more measurement occasions enable examining temporal dynamics between changes, which are more informative of causal relations. Few longitudinal studies so far have collected data on brain structure and function from more than two measurement occasions, but such studies will likely increase in the upcoming years.

Others have expressed a need for more objective measures of activity engagement, and better harmonization of measures across studies so that results can more easily be aggregated across studies in meta-analyses (Bielak, 2010; Fallahpour et al., 2016; Prakash et al., 2015; Yates et al., 2016). Although objective measures of physical activity are clearly useful and feasible, finding objective measures of leisure activities engagement is more difficult. The repertoire of leisure activities is highly dependent on cultural socialization (and therefore varies by birth cohort), socio-economic factors, gender, and other background factors (Kleiber & Genoe, 2012) as well as on individual strengths and limitations and preferences (Desai, 2011). Any objective measure must therefore be capturing engagement beyond concrete lists of activities. An interesting example is the use of GPS tracking of participants and integrating information on the means of transportation (e.g. car, train), the range of mobility (how far from home, how much travelling), and the nature of the places visited (shopping center, relatives, church). However, as we have learned from **Study III**, subjective measures can be informative, too. Inter-individual differences in subjective experience, such as we have seen in the participants' ratings of their intensity in engaging in physical activity, were related to differences in cognitive performance and DA signaling in the brain. These findings suggest that how intensely a person perceives his or her physical activities has a bearing not only on cognition, but also on brain neurochemistry. An interesting way to move forward with measurement of lifestyle and cognition in a more ecologically valid way might be offered by measurement-burst designs using mobile devices (Sliwinski, Almeida, Smyth, & Stawski, 2009).

With new technologies, masses of data amount. One present and future challenge is to harmonize databases in a way that makes them useful. Another challenge will be to meaningfully combine theory-driven approaches with data-mining in the endeavor to use large databases to search for answers to long-standing research questions within brain aging and cognitive aging research. To this end, approaches such as SEM trees and forests should be further probed and refined.

Although new means of data collection and techniques of data mining enable us to extract the most information from observational data, it is crucial that more intervention studies establish which components of lifestyle choices are causally related to aging-related changes in brain and cognition. This will be of interest not only for the general public with regard to lifestyle recommendations, but also for researchers in order to further understand the process of cognitive and brain aging. On the basis of the existing literature and the results from this thesis, it seems reasonable to recommend staying physically active in order to remain cognitively healthy. Even though the evidence is not unequivocally in favor of physical activity as protective against cognitive decline (Young et al., 2015), the possible health benefits outweigh the risks, overall. For other types of leisure activities, the evidence is not conclusive, which is partly due to the fact that it is difficult to investigate effects of complex patterns of lifestyle choices. For any given individual, the choices of how to fill time with meaning are important and will potentially make a difference also with regard to cognitive changes, given the specific circumstances and options.

6 ACKNOWLEDGEMENTS

I am very glad I ended up with my main supervisor **Martin Lövdén**. You gave me a lot of freedom while you still took responsibility, you were approachable, personal, and always supportive – thus provided a perfect basis for me to grow as a researcher, and as a person. You did not only transfer lots of your skills and knowledge to me, but were also a role model of a great supervisor and group leader for the lab you successfully built up during my time as a PhD student. Your ability to focus on the important issues without losing your open-mindedness will stick with me.

On top, I had a group of very helpful and approachable co-supervisors. **Lars Bäckman**, thank you for your sharp-witted comments, open-mindedness and schedule flexibility in end phase of the work. **Yvonne Brehmer**, thank you for being encouraging throughout the whole process. **Erika Jonsson Laukka**, your ability to keep track of all the details and see the bigger picture at the same time impressed me.

I enjoyed a very pleasant work environment at ARC with a group of knowledgeable and skilled colleagues. Thanks to **everyone at ARC**. Special thanks to **Laura Fratiglioni**, head of ARC for most of the time during my thesis, and PI of SNAC-K. It was always inspiring to talk to you, thank you for staying involved in my work on SNAC-K data and for your always valuable input. Special thanks to **Tina Kiderud** for good advice and practical help with the rating questionnaire used in Study II and IV. Importantly, without the people doing the real work, this thesis would of course have been impossible. I am very grateful to **all participants** in SNAC-K and COBRA, and to **the persons that collected and managed the data**.

Also, thanks to everyone in the **psychology group**, for good discussions in the Psycho-Fika, in the kitchen, and on our retreats. **Goran Papenberg**, you have been such a helpful, and sociable, colleague throughout the years. Thanks also to the **COBRA group** for all I learned about dopamine, PET, multimodal brain imaging, and more, and for being enjoyable to work with, with special credit to **Lars Jonasson** who was always quick, concrete, and knowledgeable in replying to any questions.

Special thanks to **Andreas Brandmaier** for introducing me to SEM trees, for making me curious about data mining, machine learning, and prediction, and for the work on Study IV – to be continued! I very much enjoyed the fruitful and productive collaboration with further co-authors and

colleagues, **Micael Andersson**, **Jan Axelsson**, **Amaia Calderón-Larañaga**, **Beata Ferencz**, **Grégoria Kalpouzos, Nina Karalija**, **Tie-Qiang Li**, **Ulman Lindenberger**, **Lars Nyberg**, **Katrine Riklund**, **Alireza Salami**, **Giola Santoni**, **Anders Wåhlin**, **Hui-Xin Wang**, **Rui Wang**, and **Anna-Karin Welmer.**

Invaluably helpful with administrative work on a daily basis were **Vanessa Suthat** and **Cecilia Annerholm,** and all other administrators – always unbelievably friendly and nice! Thanks also to **Kimberly Kane** for teaching me a lot about scientific writing.

Very important persons on a day-to-day basis were my room-mates and friends **Martin Bellander**, **Rasmus Berggren**, **Nina Becker**, and **Lieke de Boer**. I benefitted so much from your curiosity, sharpness, and friendship, all the good questions and all the important and unimportant discussions. Heja på er! Martin och Rasmus, tack för att lära mig svenska, R, och mycket mer.

I am grateful to my beloved parents **Heinke Hachmann-Köhncke** and **Hans-Hinrich Köhncke** and **my whole family** for unconditional love and support. To **all my friends** outside work for enriching my life. Special credits to my friend **Anna-Maria Hilborn** for the artwork on the cover. **Margret Karsch,** thank you for being my closest ally and toughest opponent, and for all the love. Lastly, my dear child **Pelle**, who accompanied the thesis in a parallel process of development: you constantly reminded me of the most important things in life.

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8 APPENDIX

LIST OF DISSERTATIONS FROM THE AGING RESEARCH CENTER AND THE STOCKHOLM GERONTOLOGY RESEARCH CENTER, 1991-2017

1991

Herlitz Agneta. Remembering in Alzheimer's disease. Utilization of cognitive support. (Umeå University)

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 dementia disorders: 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.

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. Findings from a population survey.

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 years and above. (Licentiate thesis)

1999

Almberg Britt. Family caregivers caring for relatives with dementia – Pre- and post-death experiences.

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. 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 population-based study.

Jonsson Laukka Erika. 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)

Nordberg Gunilla. Formal and informal care in an urban and a rural population. Who? When? What?

Beckman Gyllenstrand Anna. Medication management and patient compliance in old age.

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.

Xu Weili. Diabetes mellitus and the risk of dementia. A population-based study.

Meinow Bettina. Capturing health in the elderly population – complex health problems, mortality, and the allocation of home help services. (Stockholm University)

Agahi Neda. Leisure in late life. Patterns of participation and relationship with health.

Haider Syed Imran. Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

2009

Thilers Petra. The association between steroid hormones and cognitive performance in adulthood.

Masud Rana AKM. The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh

Paillard-Borg Stéphanie. Leisure activities at old age and their influence on dementia development.

Livner Åsa: Prospective and retrospective memory in normal and pathological aging.

Atti Anna-Rita. The effect of somatic disorders on brain aging and dementia: Findings from population-based studies.

2010

Fors Stefan. Blood on the tracks. Life-course perspectives on health inequalities in later life.

Keller Lina. Genetics in dementia. Impact in sequence variations for families and populations.

2011

Schön Pär. Gender matter. Differences and changes in disability and health among our oldest women and men.

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

Rieckmann Anna. Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

2012

Haasum Ylva. Drug use in institutionalized and home-dwelling elderly persons.

Mangialasche Francesca. Exploring the role of vitamin E in Alzheimer's disease. An epidemiological and clinical perspective.

Lovén Johanna. Mechanisms of women's own-gender bias and sex differences in memory for faces.

2013

Hooshmand Babak. The impact of homocysteine and B vitamins on Alzheimer's disease, cognitive performance and structural brain changes.

Rizzuto Debora. Living longer than expected: protective and risk factors related to human longevity.

2014

Sjölund Britt-Marie. Physical functioning in old age: Temporal trends and geographical variation in Sweden.

Wastesson Jonas. Unequal drug treatment: age and educational differences among older adults.

2015

Sköldunger Anders. Dementia and use of drugs: Economic modelling and population-based studies.

Craftman Åsa Gransjön. Medicine management in municipal home care; delegating, administrating and receiving.

Svärd Joakim. Emotional facial processing in younger and older adults.

Wang Rui. Cardiovascular risk factors, brain structure, and cognitive decline in old age.

Pantzar Alexandra. Cognitive performance in old-age depression.

2016

Kelfve Susanne. Gotta survey somebody: methodological challenges in population surveys of older people.

Heap Josephine. Living conditions in old age: Coexisting disadvantages across life domains.

Håkansson Krister. The role of socio-emotional factors for cognitive health in later life.

Behnaz Shakersain. Impact of nutritional status and diet on cognitive decline and survival.

Bellander Martin. Plasticity of memory functioning: genetic predictors and brain changes.

2017

Ferencz Beata. Genetic and lifestyle influences on memory, brain structure and dementia.