# Cognitive Plasticity in Healthy Older Adults:
# Effects of Nonpharmacological Interventions and Predictors of Intervention Success

Inauguraldissertation

zur

Erlangung des Doktorgrades

der Universität zu Köln

nach der Promotionsordnung vom 10.05.2010

vorgelegt von

**Mandy Roheger, M.Sc.**

aus Herne

Köln 2019

1.Berichterstatterin: Prof. Dr. Hilde Haider (Köln)

2. Berichterstatterin: Prof. Dr. Elke Kalbe (Köln)

Diese Dissertation wurde von der Humanwissenschaftlichen Fakultät der Universität zu Köln im Dezember 2019 angenommen.

Tag der mündlichen Prüfung: 19.12.2019

## Summary

**Background:** Even in the absence of health problems, the ageing process is associated with deficits in cognitive functioning. One way to maintain cognitive abilities in healthy older adults is the participation in cognitive training (CT) interventions or combined cognitive and physical training (CPT) interventions. However, so far it is unclear, which of these non-pharmacological interventions is the most efficient. Furthermore, one question that also has not been properly investigated is: Who benefits most from these non-pharmacological interventions? So far, data is rare and inconsistent regarding which specific characteristics of individuals predict success of CT and CPT. Yet, this knowledge is highly relevant as it would facilitate the design of new, optimally tailored programs for subgroups to ensure individual-centered prevention of cognitive decline in the age of personalized medicine.

**Aims:** The overall aims of this thesis were (i) to investigate whether CT and CPT can help healthy older individuals to maintain or even improve their cognitive functions and (ii) to identify possible factors that determine who benefits most from CT and/or CPT directly after an intervention and at follow-up one year later.

**Methods:** The thesis comprises four studies. Study I was a partly randomized controlled trial comparing the effectiveness of a structured CT ($n$ = 35 healthy older individuals) with an unstructured CT ($n$ = 35) and a passive control group ($n$ = 35) directly after the intervention. This study identifies predictors of CT success. Study II investigates the effectiveness of a CT ($n$ = 23 healthy older individuals) compared to a CPT ($n$ = 28) and a CPT plus counselling ($n$ = 30) one year after the intervention. Furthermore, possible predictors for CPT success one year after the intervention were investigated. Study III focuses on predictors of short- and long-term CT success. Analyses of Study II and Study III were based on the same data. Study

IV is a systematic review of studies ($n$ = 28) investigating predictors of memory training success in healthy older individuals.

**Results:** The main results of Study I showed that attending a structured CT was more effective than attending an unstructured CT and no intervention (the control group) to improve verbal short-term memory. Results of Study II showed a significant effect favouring the CPT in comparison to CPT plus counselling in the domains overall cognition and verbal long-term memory. Also, within-group comparisons showed cognitive improvements for all types of training. Regarding predictors of CT and CPT success in healthy older individuals, results of Studies I, II and III show that "more vulnerable" groups (i.e., individuals with less education, at an older age, and with worse performance on neuropsychological tests at training entry) can benefit more from CT as well as from CPT both directly after the training and one year later. The systematic review conducted in Study IV revealed that the statistical analyses and dependent variables used to calculate predictors of memory training success differ greatly and may explain the partly conflicting results regarding predictors of training success in the existing literature.

**Conclusion:** The present thesis contributes to the research into the effectiveness of CT and CPT interventions by showing that both CT and CPT interventions are suitable for maintaining and improving cognitive functions in healthy older adults. Furthermore, substantial contributions were made to the investigation of possible predictors of CT and CPT success, thus taking an important step toward an individualized prevention approach to maintaining cognitive abilities in healthy older ageing. Moreover, the identification of methodological shortcomings in prediction research so far will contribute to the establishment of guidelines and a higher methodological quality of future prediction research.

**Content**

# I Studies included in the cumulative thesis

This thesis is based on the following publications, which are referred to in the text by their roman numerals (Study I–IV).

**I.** **Roheger**, M., Kessler, J., & Kalbe, E. (2019). Structured Cognitive Training Yields Best Results in Healthy Older Individuals, and Their ApoE4 State and Baseline Cognitive Level Predict Training Benefits. *Cognitive and Behavioral Neurology: Official Journal of the Society for Behavioral and Cognitive Neurology*, 32, 76.

**II.** Kalbe, E.[1], **Roheger, M.[1],** Paluszak, K., Meyer, J., Becker, J., Fink, G. R., ... & Kessler, J. (2018). Effects of a Cognitive Training With and Without Additional Physical Activity in Healthy Older Individuals: A Follow-Up 1 Year After a Randomized Controlled Trial. *Frontiers in Ageing Neuroscience,* 10.

**III.** **Roheger, M**., Meyer, J., Kessler, J., & Kalbe, E. (2019). Predicting short-and long-term cognitive training success in healthy older individuals: who benefits? *Ageing, Neuropsychology, and Cognition*, 1-19.

**IV.** **Roheger, M.,** Folkerts, A.-K., Krohm, F., Skoetz, N., & Kalbe, E. (2019). Prognostic factors for memory training success in healthy older individuals: A systematic review and outline of statistical challenges. *Unpublished Manuscript*.

[1]both authors contributed equally.

# II Additional Papers

The author has contributed to the following publications or manuscripts that are not included in the thesis:

**Roheger, M.**, Eriksdotter, M., Westling, K., Kalbe, E., & Garcia-Ptacek, S. (2019). Diagnostic Work-Up Is More Complete in Rural than in Urban Areas for Patients with Dementia: Results of a Swedish Dementia Registry Study. *Journal of Alzheimer's Disease*, 1-8.

**Roheger, M.**, Zupanic, E., Kåreholt, I., Religa, D., Kalbe, E., Eriksdotter, M., & Garcia-Ptacek, S. (2018). Mortality and nursing home placement of dementia patients in rural and urban areas: a cohort study from the Swedish Dementia Registry. *Scandinavian Journal of Caring Sciences*, *32*, 1308-1313.

Folkerts, A. K., Dorn, M. E., **Roheger, M.**, Maassen, M., Koerts, J., Tucha, O., ... & Kalbe, E. (2018). Cognitive Stimulation for Individuals with Parkinson's Disease Dementia Living in Long-Term Care: Preliminary Data from a Randomized Crossover Pilot Study. *Parkinson's Disease*, *2018*.

**Roheger, M.**, Kalbe, E., & Liepelt-Scarfone, I. (2018). Progression of cognitive decline in Parkinson's disease. *Journal of Parkinson's Disease*, *8*, 183-193.

Folkerts, A. K., **Roheger, M.**, Franklin, J., Middelstaedt, J., & Kalbe, E. (2017). Cognitive interventions in patients with dementia living in long-term care facilities: Systematic review and meta-analysis. *Archives of Gerontology and Geriatrics*, *73*, 204-221.

# III List of Abbreviations

| | |
|---|---|
| AD | Alzheimer's disease |
| apoE-4 | Apolipoprotein E-4 |
| BDI | Beck's Depression Inventory |
| BDNF | Brain derived neurotrophic factor |
| CI | Confidence Interval |
| CT | Cognitive Training |
| CPT | Combined Cognitive and Physical Training |
| DemTect | Demenz-Detektionstest |
| IGF-1 | Immune-globulin factor1 |
| MF | Mentally Fit |
| MCI | Mild cognitive impairment |
| MRI | Magnetic Resonance Imageing |
| NV | NEURO*vitalis* |
| PT | Physical Training |
| RCT | Randomized controlled trial |
| SMD | Standardized Mean Difference |
| tDCS | Transcranial direct-current stimulation |
| TMS | Transcranial magnetic stimulation |
| WHO | World Health Organization |
| VEGF | Vascular endothelial growth factor |

# IV List of Tables

# V List of Figures

# 1. Introduction

Even in the absence of health problems, the ageing process is associated with deficits in cognitive functioning, resulting in a loss of autonomy and quality of life in older adults in the long term (Reuter-Lorenz & Park, 2014). Given the demographic changes our society is facing (Megyesiová & Hajduová, 2012), upcoming challenges on how to maintain cognitive functions to ensure an independent, high-value life even in old age is an important area of research (Sandberg, Rönnlund, Derwinger-Hallberg, & Stigsdotter Neely, 2016). Nonpharmacological interventions have gained increased interest in the context of healthy ageing processes and dementia prevention (Livingston et al., 2017). One way to maintain or even improve cognitive abilities in the context of nonpharmacological interventions is participation in cognitive training (CT), physical training (PT), or combined cognitive and physical (CPT; Cespón, Miniussi, & Pellicciari, 2018). There is accumulating evidence that all three types of intervention have positive effects not only on general cognition in healthy older participants, but also on the improvement of the quality of life and reduction of depressive symptoms (Chiu et al., 2017; Joubert & Chainay, 2018; Northey, Cherbuin, Pumpa, Smee, & Rattray, 2018). However, the effects regarding the different cognitive domains affected by the training and their underlying mechanisms are still under debate and need more research.

Furthermore, one question that has not been properly investigated is: Who benefits most from these non-pharmacological interventions? So far, data is rare and inconsistent regarding which specific characteristics of individuals predict success of CT and CPT. Yet this knowledge is highly relevant because the identification of factors improving or even maintaining training effects of CT and CPT could be used to decide which nonpharmacological training program is best suited for a specific individual (Langbaum, Rebok, Bandeen-Roche, & Carlson, 2009). Furthermore, this would facilitate the design of new, better, optimally tailored programs for subgroups to ensure individual-centered prevention of cognitive decline.

Therefore, the present thesis (i) investigates whether CT and CPT can help healthy older adults to maintain or even improve their cognitive functions, and (ii) tries to identify possible factors that determine who benefits most from CT and CPT. In the following chapters, evidence on cognitive changes in healthy ageing will be introduced with a special focus on inter-individual changes in the healthy ageing process, as well as neural, structural, and cognitive changes in the ageing brain. Furthermore, definitions of CT, PT, and CPT will be provided and their effectiveness, as well as neurophysiological mechanisms underlying cognitive improvement for each training type, will be discussed. Additionally, an overview of possible predictors for CT and CPT training success in healthy older adults will be presented and different theories regarding their effectiveness will be introduced. Further, the importance of prediction research in general will be highlighted. The Introduction concludes with a detailed evaluation of the general research questions and hypothesis of the thesis at hand.

## 1.1 Cognition and cognitive changes in healthy ageing

In the 2020s, one quarter of the population worldwide will be 65 years and older (Bherer, 2015). This demographic development has an overwhelming societal impact, as it presents a challenge in managing health care due to the physical and psychological changes associated with ageing (Blazer, Yaffe, & Liverman, 2015). One of the most feared aspects of ageing is cognitive decline (Deary et al., 2009). Cognition in general comprises the mental functions involved in attention, thinking, understanding, learning, remembering, solving problems, and making decisions (Glisky, 2007). Cognitive decline consistently is defined as “developing worsened thinking, language, memory, understanding, and judgement” (Deary et al., 2009, p. 6).

Nevertheless, a clear definition of a healthy, non-pathological ageing process is still lacking and individual differences in neuronal, structural, and cognitive changes in the ageing brain have to be remembered and taken into account when conducting research on cognitive changes in healthy older adults. Therefore, in the next paragraphs, a definition of healthy cognitive ageing is introduced and reasons for and consequences of differences in inter-individual cognitive ageing are discussed. In the last two paragraphs of this section (1.1.3 and 1.1.4) neuronal, functional, structural, and cognitive changes in the healthy ageing brain (which – even though there is a high variation in the ageing process experienced by each individual - occur in every individual albeit to different degrees) are presented.

### 1.1.1 Healthy cognitive ageing: A definition attempt

To date, distinguishing between healthy and pathological ageing in the human brain is challenging, even impossible (Brayne, 2007). Yet it is acknowledged and must be kept in mind that individual differences in cognitive ageing cannot be classified into distinctive groups (as is needed for treatment decisions), but occur along a continuum (Deary et al., 2009). Therefore, modern diagnostic schemes (Jack et al., 2011) try to define this continuum of possible syndromes in cognitive ageing, ranging from *ageing with normal cognitive changes*[1] (defined by "the subtle loss of cognitive and functional performance that occurs in normal ageing, even when known brain diseases are absent" (Smith, 2016)), to *preclinical states* (which "involve biomarker measurement of brain changes in people with neurodegenerative diseases years before they show measureable behavioral manifestations of the disease" (Smith, 2016)), to *mild cognitive impairment* (MCI; a syndrome characterized by "deficits in memory or other cognitive functions with intact performance in activity of daily

[1] Please note that the author acknowledges the diversity of individual ageing, thus refusing an artificial normativity approach assigned to the process. The standardized model reflects white-western-male hegemony, not taking into account for example social, gender, economic, and class differences and their influences on individual ageing processes. Therefore the standard model needs to be replaced by individual, critical approaches acknowledging the mentioned circumstances of an individuals' life (for more information, please see Spector-Mersel (2006); Henrich, Heine, and Norenzayan (2010); Marshall (1995)).

living tasks" (Winblad et al., 2004)), and up to *dementia* (a syndrome of clear cognitive and functional decline (Smith, 2016)).

In the present thesis, individuals who "age with normal cognitive changes" (as defined by Jack et al., 2011) are investigated and operationalized as individuals with normal or corrected-to-normal vision and hearing as well as the absence of any past or present psychiatric or neurological diseases (assessed via self-report). Individuals with chronic diseases were not excluded, because assuming that biological age is different from chronological age and defined as healthy ageing, samples that exclude those individuals with age-related pathology will not be representative (Brayne, 2007). It is important, however, to keep in mind that within the range defined by *ageing with normal cognitive changes* individuals still differ greatly in their degree of cognitive functioning (Hedden & Gabrieli, 2004) and that the points on the continuum that are deemed pathological or not can change according to the operationalization used in studies (Deary et al., 2009). Therefore, in the present thesis, the operationalization of "healthy older individuals" was retained over all conducted studies.

### 1.1.2 Inter-individual differences in healthy cognitive ageing

On an inter-individual basis, there is a great variation in age-related changes in brain function, structure, and cognition (Glisky, 2007). Inter-individual differences in the cognitive ageing process seem to reflect two major themes: (i) differences in prior cognitive abilities gained throughout the life, and (ii) differences caused by brain deterioration that has already taken place (Deary et al., 2009). Cross-sectional studies have shown that different life experiences (e.g. lifetime occupation), genetic influences, education, and an active lifestyle (mentally, physically, and socially) all impact the cognitive performance of older individuals (e.g. Bäckman & Nyberg, 2013; Rapp & Amaral, 1992). However, up to now, not much is known about the underlying mechanisms of these inter-individual differences in cognitive ageing (Brehmer, Kalpouzos, Wenger, & Lövdén, 2014). As a consequence, most investigated samples of healthy older adults are highly heterogeneous regarding these inter-individual differences and their cognitive status along the continuum of healthy ageing (Jockwitz et al., 2019). Hence, it is important to acknowledge that changes in cognition and brain ageing reported in studies may vary according to sample selection (Baltes, 1993). Future research should emphasize the investigation of individual differences (Hedden & Gabrieli, 2004) to deepen our understanding of which individuals can benefit from a specific intervention to support non-pathological cognitive ageing (Brehmer et al., 2014).

### 1.1.3 Neural changes in the healthy ageing brain

Every adult experiences neural, structural, and functional age-related changes that reflect intra-individual differences in magnitude and pace of these changes (Jockwitz et al., 2019). The brain undergoes distinctive age-related changes (Raz & Rodrigue, 2006). Brain atrophy, a steady decrease in brain size due to a loss of white and grey matter, is one of the most obvious (Bender, Völkle, & Raz, 2016). At the same time, atrophy is balanced by an increase in ventricular spaces and cerebrospinal fluid (Grady, 2008). Brain atrophy shows an anterior-posterior gradient with some regions, such as the prefrontal cortex, being particularly affected (Buckner, 2004). Yet, this decline in volume of grey and white matter is not caused by cell death, but by lower synaptic densities (Terry, 2000). Between the ages of 20 and 100 years, neocortical synapse density declines steadily (Hedden & Gabrieli, 2004), and – by the age of 130 years – the synaptic density of a non-demented, healthy, aged adults would reach the reduced density that is seen in individuals affected by Alzheimer's disease (AD; Terry & Katzman, 2001). Because of individual differences seen in brain ageing, it is a complex task to map structure to function and change owing to the ageing process (Peters, 2006). There are some studies, however, showing links between volume and neuropsychological function (Gallagher & Rapp, 1997). There is also good news regarding age-related changes in the human brain: accumulating evidence exists that the brain offers the potential of plasticity (Brehmer et al., 2014). Neuroplasticity is defined as “the ability of the brain and central nervous system to adapt to environmental change, respond to injury and to acquire novel information by modifying neural connectivity and function” (Knaepen, Goekint, Heyman, & Meeusen, 2010). Therefore, research on interventions with the aim of ensuring healthy ageing is often based on the concept of neuroplasticity (Zhu, Yin, Lang, He, & Li, 2016).

To summarize, several structural, neural, and functional changes occur in the healthy ageing brain. These changes cannot be regarded as isolated processes, but as reciprocal processes along an inter- and intra-individual continuum in ageing, affecting, for example, structure, functionality, behavior, and also cognition (for more detailed reviews on healthy ageing and changes in the ageing brain see, for example, Fjell, McEvoy, Holland, Dale, & Walhovd, 2014; Glisky, 2007; Raz & Rodrigue, 2006).

### 1.1.4 Cognitive changes in the healthy ageing brain

Analogous to brain ageing, age-related changes in cognition and cognitive abilities are highly inter- and intra-individual and complex, because different cognitive domains are differentially sensitive to age effects (Jockwitz et al., 2019). Furthermore, it is challenging to understand age-related changes in cognition, for several reasons:

i. As already discussed, it is difficult to separate the effects of healthy and pathological ageing (Fjell et al., 2014).
ii. Conclusions regarding the effects of ageing are always correlational, because ageing cannot be manipulated (Hedden & Gabrieli, 2004).
iii. Despite the need for long-term longitudinal studies to examine the effect of ageing in the same individuals over time, studies of ageing are mostly cross-sectional, for economic reasons (Schaie, 1993).

iv. Many brain and cognitive changes occur in parallel during ageing, therefore, it is difficult to relate particular changes in the brain to particular cognitive changes (Hedden & Gabrieli, 2004).

v. Research suggests that variance in cognitive performance follows a non-linear trend across the life span, indicating a higher inter-individual variability in older adults (Habib, Nyberg, & Nilsson, 2007; Hartshorne & Germine, 2015).

However, accumulating recent research suggests that in some cognitive functions, such as verbal ability and general knowledge, there is little age-associated cognitive decline, whereas there are some cognitive abilities, such as processing speed, executive functions, episodic and working memory, that are highly vulnerable to age-associated changes (Habib et al., 2007; Hedden & Gabrieli, 2004; Jockwitz et al., 2019; Park & Reuter-Lorenz, 2009; Schaie & Willis, 2010). Table 1 offers an overview of cognitive changes in healthy ageing.

Table 1: Overview of Cognitive Changes due to Healthy Ageing.

| Domain | Direction of Change | Comments |
|---|---|---|
| **Intelligence** | | |
| - crystalline | no change/increase | can decrease in higher age |
| - fluid | decrease | |
| **Learning and Memory** | | |
| sensory memory | small decrease | encoding time increases |
| primary memory | small decrease | |
| secondary memory | | |
| - episodic memory | decrease | problems with encoding and recall |
| - semantic memory | no chance | |
| implicit memory | no change | different results |
| prospective memory | decrease | no decrease in every-day tasks |
| **Attention** | | |
| selective attention | decrease | inconsistent results |
| sustained attention | small decrease | inconsistent results |
| divided attention | decrease | only in complex tasks |
| **Executive Functions** | | |
| strategy | decrease | |
| building concepts | decrease | |
| cognitive flexibility | decrease | |
| task-switching | decrease | |
| interference sensitivity | decrease | |
| **Language** | | |
| every-day communication | no change | only when sensory deficits occur |
| phonological, syntactical & lexical knowledge | no change | |
| word generation | decrease | |
| speech production | changes | syntactic complexity is reduced |
| speech reception | decrease | |
| **Visual-spatial abilities** | | |
| recognition of fragmented pictures | decrease | |
| visual search | decrease | |
| mental rotation | decrease | |
| visuo-construction | decrease | |
| **Cognitive processing speed** | reduced | |
| **Social Cognition** | not known | inconsistent results |

Source: Adapted from Kalbe and Kessler, 2009 (as cited in Sturm, Herrmann, & Münte, 2009).

## 1.2 Non-pharmaceutical interventions to enhance cognitive performance

A growing body of literature has provided evidence for cognitive improvements in healthy older individuals after applying non-pharmaceutical interventions (Cespón et al., 2018). Non-pharmaceutical interventions are thought to promote brain plasticity mechanisms, as reported by neuroimaging studies using animal models, as well as humans (Curlik & Shors, 2013). The development of these non-pharmaceutical interventions is highly important to prevent and prolong cognitive deficits in healthy ageing processes, but also in AD and other forms of dementia (Bamidis et al., 2014). Non-pharmaceutical interventions are mainly based on CT interventions, PT interventions, and non-invasive brain stimulations (Cespón et al., 2018). In the present thesis, the focus is solely on CT, PT and combined CT and PT interventions (CPT), as these interventions have been widely publicized and therefore provide a basis for interpretations and conclusions (Lehert, Villaseca, Hogervorst, Maki, & Henderson, 2015), and because CT and PT interventions are implemented in the everyday routine in, for example, nursing homes (for a review of non-invasive brain stimulation interventions see, for example, Tatti, Rossi, Innocenti, Rossi, & Santarnecchi, 2016). In contrast, non-invasive brain stimulation such as transcranial magnetic stimulation (TMS) and transcranial direct-current stimulation (tDCS) have just recently gained scientific interest and have not yet been implemented into clinical routines.

Therefore, in the following sections definitions for CT, PT, and CPT will be introduced, possible underlying mechanisms will be discussed, and neuropsychological evidence for the benefits of each training type will be presented. Section 1.2 concludes with a short summary and comparison of all three training interventions.

### 1.2.1 Cognitive training interventions

One difficulty regarding research on cognitive interventions is the fact that the terms cognitive training, mental activity, cognitive stimulation, cognitive rehabilitation, and cognitive exercise are used interchangeably (Buschert, Bokde, & Hampel, 2010). Clare, Woods, and colleagues (2003) have attempted to clarify the definitions and terminology on cognitive interventions by proposing two main categories: (i) cognitive stimulation/ reality orientation, which includes procedures designed to enhance an individual’s social skills and provide general cognitive stimulation, and (ii) cognitive training/cognitive rehabilitation, which includes procedures designed to train specific cognitive processes (Clare, Woods, Moniz Cook, Orrell, & Spector, 2003). The present thesis focuses on CT, defined as a standardized set of exercises (Martin, Clare, Altgassen, Cameron, & Zehnder, 2011), which involves repeated practice and is designed to reflect particular cognitive functions, such as memory, attention, or executive functions (Bamidis et al., 2014; Clare et al., 2003). CT tasks may be presented either in paper-and-pencil (Bamidis et al., 2014) or computerized (Lampit, Hallock, & Valenzuela, 2014; Millán-Calenti et al., 2015) form. The training can be performed individually or in small groups, even though the work remains on an individual level (Joubert & Chainay, 2018). The primary goal of CT is to maintain or even improve cognitive functions (Chiu et al., 2017). CT may also vary in training length, intensity, and structure (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008). The CT used in the present thesis is described in more detail in the summaries of the scientific contributions.

Many studies have reported increased cognitive performance after CT in healthy older adults in a variety of cognitive domains, such as memory (Boron, Turiano, Willis, & Schaie, 2007; Rebok, Carlson, & Langbaum, 2007; Verhaeghen, Marcoen, & Goossens, 1992), working memory (Brehmer, Westerberg, & Bäckman, 2012; Li et al., 2008), attention and speed of processing (Ball, Edwards, & Ross, 2007; Roenker, Cissell, Ball, Wadley, & Edwards, 2003), and executive control (Bherer et al., 2005). To date, several systematic reviews and meta-analyses support this evidence and show an improvement in the cognitive status after CT in healthy older individuals compared with active or passive control groups (Kelly et al., 2014; Martin et al., 2011; Papp, Walsh, & Snyder, 2009). A recent meta-analysis by Chiu and colleagues (2017) on the effect of cognitive-based trainings for healthy older adults, including 31 randomized controlled trials (RCTs) showed that CT has a moderate effect on overall cognitive functioning ($g$ = 0.42, 95% CI = 0.21 to 0.63) and executive functions ($g$ = 0.42, 95% CI = 0.24 to 0.60), and a small effect on memory ($g$ = 0.35, 95% CI = 0.24 to 0.47), attention ($g$ = 0.22, 95% CI = 0.13 to 0.31), and visuospatial abilities ($g$ =

0.18, 95% CI = 0.02 to 0.35; (Chiu et al., 2017). However, the extent to which these benefits transfer to non-trained tasks is still a matter of debate (Lee et al., 2012; Lussier, Brouillard, & Bherer, 2017).

Assumptions on the efficiency of CT are mainly based on theories of plasticity (Pascual-Leone et al., 2011). Plasticity is defined as the ability of the organism to remain modifiable throughout the life span (Bherer, 2015; Brehmer et al., 2014). The concept of plasticity has been further developed over the years to include structural changes in the brain at the cellular, molecular, and system levels (Cotman & Berchtold, 2002). *Neuronal plasticity* is defined as a specific type of plasticity on the level of neuronal networks meaning that due to the plasticity, neuronal reactivation, functional compensation, enhanced neurotransmission, and various other modifications in the neuronal network can occur (Baltes, Kühl, Gutzmann, & Sowarka, 1995; Chen, Cohen, & Hallett, 2002; Knaepen et al., 2010). Humans appear to be capable of modifying neuronal connections not only on a structural, but also on a functional level during their youth, and adulthood, even into old age (Buonomano & Merzenich, 1998). This capability seems to be the basis of the so-called cognitive plasticity (Draganski et al., 2004). *Cognitive plasticity* is defined as the individual's learning potential or as the acquisition of knowledge and development of new abilities (Calero & Navarro, 2007). It is assumed that CT "guides" plasticity on all levels by increasing the number of surviving newborn neurons and integrating new neurons and synapses into pre-existing neural networks (Bamidis et al., 2014; Curlik & Shors, 2013; Zhu et al., 2016). Neuronal processes seem to be plastic and therefore have the potential to rewire and reorganize due to CT (Smith et al., 2009). Additionally, CT may increase the overall cellular activity and metabolic rate in certain brain regions and networks, as well as overall brain volume, cortical thickness, and coherence of white-matter tracts due to cognitive plasticity (Belleville & Bherer, 2012; Bherer, 2015; Chapman et al., 2015). However, the exact mechanism of neuroplasticity (i.e., functional and structural changes) that induce cognitive plasticity after CT resulting in cognitive gains in healthy older adults still remain poorly understood (Chapman et al., 2015).

### 1.2.2 Physical training interventions

Physical training interventions usually involve a wide range of activities (Colcombe & Kramer, 2003; Kramer & Colcombe, 2018). Therefore, similar to CT, different definitions exist (Bamidis et al., 2014). The World Health Organization (WHO) defines PT as exercises that include “recreational or leisure time physical activity, transportation (e.g. walking or cycling), occupational (if the person is still engaged in work), household chores, play, games, sports, or planned exercise, in the context of daily, family, and community activities” (WHO, 2010). The German federal ministry for health published a national guideline for suggestions on physical exercise and promotion of physical exercise in which they define health-enhancing PT as any form of physical activity that benefits health and functional capacity without undue harm and risk (Rütten & Pfeifer, 2016; Foster, Hillsdon, Thorogood, Kaur, & Wedatilake, 2005).

Prospective observational studies have robustly demonstrated that physically active people have a reduced risk of cognitive decline (Erickson, Gildengers, & Butters, 2013; Scarmeas & Stern, 2003; Sofi et al., 2011) and dementia (Hamer & Chida, 2009) in advancing age. Northey and colleagues (2018) conducted a systematic review and meta-analysis including 39 RCTs on PT in healthy adults older than 50 years and showed that PT improved cognitive functions (*SMD* = 0.29, 95% CI 0.17 to 0.41). They conclude that to maintain cognitive function, individuals should attend aerobic and resistance exercise of at least moderate intensity on as many days a week as feasible (Northey et al., 2018). Barha and colleagues (2017) could show that sex differences exist regarding PT effects on improvement of cognition: the results of their meta-analysis suggest that aerobic training, resistance training, and multimodal training were associated with larger effect sizes in studies comprised of a higher percentage of women compared with studies with a lower percentage of women, suggesting that women's executive processes may benefit more from exercise than men's (Barha, Davis, Falck, Nagamatsu, & Liu-Ambrose, 2017).

Different possible explanations for the mechanisms underlying the effects of PT interventions on cognition in healthy older adults exist, yet most of them are far from being understood (Bamidis et al., 2014). Exercise-induced molecular cascades, which affect neural plasticity, may play an import role in explaining the effects of PT interventions on cognition by promoting brain vascularization, neurogenesis, and functional changes in neuronal structure (Cotman, Berchtold, & Christie, 2007; Lista & Sorrentino, 2010). Different types of exercise are thought to release different neurotrophins (proteins that support the survival, development, and overall functions of neurons) when stimulated (Northey et al., 2018; van Praag, 2009). For example, aerobic exercises have been shown to up-regulate the brain derived neurotrophic factor (BDNF; Neeper, Gómez-Pinilla, Choi, & Cotman, 1995), whereas resistance exercises seem to stimulate immune-globulin factor 1 (IGF-1) production (Cassilhas et al., 2007). Both neurotrophins are thought to improve cognitive function after PT through promotion of neurogenesis (the production of new neurons), synaptic plasticity (formation of synapses between different neurons), angiogenesis (growth of new blood vessels from already existing ones), decreased proinflammatory processes, and reduced cellular damage due to oxidative stress (Colcombe & Kramer, 2003; Cotman et al., 2007; Northey et al., 2018). Likewise, PT may have a positive effect on cognition by reducing risk factors for cognitive decline, such as cardiovascular diseases, insulin resistance, hypertension, inflammation, and amyloid plaque buildup (Adlard, Perreau, Pop, & Cotman, 2005; Carroll & Dudfield, 2004; Pedersen, 2006).

Summarizing the effects concerning CT and PT and the mechanisms underlying both trainings, the question arises how the combination of CT and PT, both of which aim at induction of positive plastic change in the brain, might jointly impact cognition in healthy older adults. Given the evidence that CT and PT influence brain structure and function, as well as cognition, one may hypothesize that a combined CT and PT approach might produce greater benefits for cognition than either form used alone (Joubert & Chainay, 2018; Lauenroth, Ioannidis, & Teichmann, 2016; Law, Barnett, Yau, & Gray, 2014)

### 1.2.3 Combined cognitive and physical training interventions

It has been proposed that combined cognitive and physical training (CPT) interventions might induce larger functional benefits on cognition in healthy older adults than each intervention on its own (Hötting & Röder, 2013; Kraft, 2012). So far, CPT studies that were conducted in healthy older adults showed mixed results (Desjardins-Crépeau et al., 2016). Studies exist that show evidence for significant benefits of CPT over CT and PT (Fabre, Chamari, Mucci, Massé-Biron, & Préfaut, 2002; Oswald, Gunzelmann, Rupprecht, & Hagen, 2006).However, also contradictory results exist demonstrating no additional cognitive enhancement after CPT when compared with CT alone (Shatil, 2013). The heterogeneity of trainings used and study designs might explain the mixed results on the effectiveness of CPT on cognition in healthy older adults so far (Desjardins-Crépeau et al., 2016). A recent systematic review by Joubert and Chainay (2018) reported that each type of training (CT and PT) seems to preferentially enhance different cognitive functions and showed superiority of CPT compared with CT and PT alone. Joubert and Chainay stated, however, that the current state of knowledge does not permit any definitive conclusions. Because CPT seems to generate more synergistic beneficial changes in the brain than either training individually, there is a need to take both trainings, CT and PT, into account when designing new and effective intervention studies which want to take advantage of the compensatory mechanisms of healthy older adults (Bamidis et al., 2014; Kraft, 2012).

The present thesis focuses only on CT and CPT intervention and not on pure PT as the combination of CT and PT seems to be more promising in maintaining cognition in the healthy ageing process.

## 1.3 Predictors of training intervention success in healthy ageing

Surprisingly few studies have addressed the question who benefits most from CT or CPT, given the large number of studies evaluating the effect of CT and CPT, the accumulating evidence for their effectiveness, and the importance of considering individual differences in training response (Sandberg et al., 2016). Possible prognostic factors/predictors[2] for CT intervention success that are under debate are sociodemographic factors, genetic parameters, and blood factors, as well as personality traits and cognitive abilities at entry to the training (Park et al., 2018). However, a systematic evaluation and summary of these factors has not so far been conducted (Fairchild, Friedman, Rosen, & Yesavage, 2013), a classification of prognostic factors and models in general is still missing, and a classification of different prognostic factors and models regarding different trainings (CT and CPT) has not yet been conducted (Riley et al., 2019). Even though research on prognostic factors/predictors of CT and/ or CPT success in healthy older adults is still in the fledgling stages, Section 1.3 that follows provides an overview of investigated predictors of CT and CPT success in healthy older adults and outlines the need for and importance of prognostic research in the context of dementia prevention and clinical decision making.

### 1.3.1 Overview of predictors of training intervention success in healthy ageing

Several variables are under discussion to be predictors for CT and CPT success, namely sociodemographic factors (age, sex, education), cognitive abilities at entry to training, genetic parameters (apolipoprotein E-4 [apoE-4]), blood factors (levels of insulin-like growth factor 1

[2] The terms “prognostic factors” and “predictors” can be used interchangeably in the context of prediction research on CT and CPT success.

[IGF-1], brain-derived neurotrophic factor [BDNF], and vascular endothelial growth factor [VEGF]). The following paragraphs provide a first unsystematic overview of the current knowledge on CT/ CPT success predictors and possible theories and explanations for their effect.

One of the most investigated variables as a predictor for CT success is age. Studies report more advanced age as a positive predictor for CT success in healthy older adults (Brooks, Friedman, Pearman, Gray, & Yesavage, 1999a; Park et al., 2018). However, contradictory results exist, indicating that younger individuals benefit more from CT (Verhaeghen et al., 1992). This result may be explained by the concept of cognitive reserve (Stern, 2012). Cognitive reserve is defined as individual differences in the neural network underlying the performance of any task, which determines the coping ability and cognitive strategy against brain pathology (Park et al., 2018; Stern, 2012). Therefore, it may not be the absolute number of years an individual lives that determines performance and improvement on a trained task, but the ability of the underlying neural networks of that individual. Contradictory results of prediction of the outcomes of training studies may then be explained with the fact that the makeup of the samples differed between the studies in the amounts of cognitive reserve in the individuals in each sample. However, this explanation has not yet been properly investigated.

The impact of sex on training-related cognitive outcomes is under-investigated (Rebok et al., 2013). Yet, Beinhoff and colleagues (2008) proposed an assumption of sex-specific plasticity, which suggests that domain-specific plasticity induced by cognitive interventions exists in women and men with AD and MCI, but also in healthy older individuals (serving as a control group in this particular study). Significant sex differences in healthy older adults have been reported, showing advantages for female individuals in the domain verbal episodic memory, and advantages for male individuals in the domain visuospatial activities (Beinhoff, Tumani, Brettschneider, Bittner, & Riepe, 2008). Munro and colleagues (2012) also showed sex differences in patterns of cognitive test performance, showing that women performed better than men on tests of psychomotor speed and verbal learning and memory, whereas men outperformed women on tests of visuoconstruction and visual perception (Munro et al., 2012).

Few studies have investigated the association between education and CT success, and these have shown conflicting results. Although some studies showed that individuals with fewer years of education improved after training (Park et al., 2018), Rebok et al. (2013), for example, found that healthy older adults with more years of education showed benefits in memory performance after CT. Notably, both directions of the effect seem plausible: on the one hand, according to the compensation hypothesis (Lövdén, Brehmer, Li, & Lindenberger, 2012), it could be possible that healthy older adults with less education benefit more, as there is more "room for improvement". On the other hand, it could also be the case that individuals with more education benefit most from CT, as education is a driver of cognitive and neural plasticity (Mandolesi et al., 2017). Furthermore, the magnification approach suggests that individual differences in gains from CT can be "explained by initial differences in cognitive resources available to acquire, implement, and sharpen effortful cognitive strategies" and therefore group differences should be magnified after training (Lövdén et al., 2012).

Personality traits as predictors for CT or CPT training success are only rarely investigated. So far, only one study has shown that Openness to Experience (taken from the NEO-Personality Inventory score that examines a person's Big Five personality traits: openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism; Fruyt, McCrae, Szirmák, & Nagy, 2004) was positively correlated to training gain (Finkel & Yesavage, 1989). This finding suggests that older participants profit more from training when they maintain their enthusiasm and ability to learn from new ventures. Further research is necessary, however, that includes different measurements for personality traits to draw conclusions from these findings.

One further result is that lower cognitive abilities at entry to training are predictive of CT improvement in healthy older adults (López-Higes et al., 2018; Whitlock, McLaughlin, &

Allaire, 2012). This might also be explained by the compensation hypothesis (Lövdén et al., 2012), which posits that participants who are already functioning at optimal levels have less room for improvement in CT performance. Accordingly, participants who start with an initially lower performance will gain more from CT. It is not entirely clear under which conditions this account may or may not be applicable and also statistical challenges regarding prediction methods exist (e.g., regression to the mean), which need to be taken into account when interpreting the results. Notably, also contradictory results exist showing that participants with initially higher cognitive abilities at entry to training benefit most from CT in healthy older adults (Fairchild et al., 2013), which may be a result of different levels of difficulty of the trainings used or can also be explained with the magnification approach (Lövdén et al., 2012).

ApoE-4, which is a class of proteins involved in the metabolism of fats in the body, is a further possible predictor for gains after CT. ApoE-4 is a known risk factor for AD (Liu, Liu, Kanekiyo, Xu, & Bu, 2013), but its negative effects on cognitive functions in healthy younger (Nao et al., 2017) and older individuals have also been reported (Wisdom, Callahan, & Hawkins, 2011). Only a limited number of studies have investigated the effects of apoE-4 on CT gains. For example, Feng et al. (2015) reported an impact of apoE-4 on CT benefits in healthy older adults, showing that apoE-4 is associated with reductions in the domain executive function and training may attenuate declines in processing speed (Feng et al., 2015).

IGF-1 is a protein that plays an important role in the regulation of adult neurogenesis (Fernandez & Torres-Alemán, 2012; O'Kusky & Ye, 2012) and is also under discussion as a possible predictor for CT and CPT gains. Deleting the IGF-receptor gene in mice, for example, results in an almost complete loss of the dentate gyrus, which is part of the hippocampus and essential for learning and memory (Liu, Ye, O'Kusky, & D'Ercole, 2009). Higher levels of IGF-1 seem to play an important role in benefits from CT, although evidence in the domain of CT and/or CPT is still lacking.

A further possible predictor for CT and CPT improvement is BDNF. BDNF is a protein that is highly concentrated in the hippocampus but is also distributed throughout the entire brain (Murer, Yan, & Raisman-Vozari, 2001). BDNF is considered to mediate the effects of exercise on synaptogenesis, synaptic plasticity, and enhanced learning and memory (Cotman et al., 2007) and therefore plays an essential role in regions that are vital to learning and memory (Bekinschtein et al., 2008). Voss and colleagues (2013) showed that higher blood levels of BDNF were associated with a greater change in functional connectivity as measured with structural and functional magnetic resonance imaging (MRI) in a group of healthy older adults who were trained with non-aerobic exercises in a CPT intervention (Voss et al., 2013). Remarkably, a possible role of BDNF in CT effects has also been investigated in clinical samples (e.g., Parkinson's disease (Angelucci et al., 2015), and MCI (Nascimento et al., 2015)), and some studies have investigated BDNF as a predictor for pure CT success in healthy older adults (Jiang et al., 2018).

VEGF is also a possible predictor of CT and CPT success. VEGF is a signal protein that stimulates the formation of blood vessels (for a detailed review on how VEGF is released in the brain and interacts with BDNF and IGF-1 see, for example, Livingston et al., 2017). Voss and colleagues (2013) found that increased VEGF after an aerobic walking intervention was associated with improved connectivity between temporal lobe structures. However, no cognitive changes were assessed in the study. Overall, the influence of VEGF as a predictor in CT and/or CPT success in healthy individuals needs more consideration.

Summarizing, results regarding predictors of CT and CPT success are partly conflicting and several possible explanations regarding their effects exist. Yet, present research does not differentiate between predictive factors (single variables) or models (multiple variables that interact with each other). Furthermore, research in general on predictors of success of CT is lacking, not to mention the lack of CPT prediction research. Also, several more predictors (e.g. personality traits, motivation, neuro-imaging) could play an important role in predicting

CT and/or CPT success, which have not been studied in detail so far. A systematic overview including not only theoretical but also statistical approaches used to determine possible predictors is urgently needed to clarify these inconsistent results and to shed light on this important issue.

### 1.3.2 Importance of prediction/prognostic research

In regard to this longstanding debate in the literature on ageing, a more detailed examination of mechanisms underlying the ability to benefit from CT and CPT interventions is especially informative (Fandakova, Shing, & Lindenberger, 2012) and is of outstanding importance for health care decision making. Specifically, the identification of factors that predict training success could inform which among alternative trainings is best suited to a given individual (Sandberg et al., 2016), thereby pointing in the direction of personalized, individual-centered medicine. Also, the knowledge of what factors drive the training effect is valuable for designing new training programs (Bissig & Lustig, 2007; West & Hastings, 2011). The flipside to the identification of individuals who benefit most from training is the identification of individuals who do not benefit at all (Fairchild et al., 2013). Many, but not all individuals have achieved cognitive improvement through CT and CPT programs (Shin, Lee, Yoo, & Chong, 2015). However, a deeper understanding of the underlying mechanisms of predictors for CT and CPT improvement and a better evaluation of possible predictors of different forms of CT and CPT may help to find an individual-based training approach for everyone and therefore contribute to the aim of preventing cognitive decline due to age-related processes.

## 1.4 Scientific research questions

The overall aims of the thesis are (i) to investigate, whether CT and CPT can help healthy older adults to maintain or even improve their cognitive functions, (ii) to identify possible factors to determine who benefits most from CT and/or CPT, and (iii) to summarize evidence on predictors of memory training success. In particular, the present thesis examines the following research questions:

i. Are CT and CPT effective in improving or maintaining cognitive functions in healthy older adults?
   a. Is a scientifically based, structured CT more effective than either an unstructured brain jogging program or no intervention in a passive control group in improving or maintaining cognitive functions (verbal memory, attention, and executive functions) in healthy older adults **(Study I)**?
   b. Is CPT more effective than pure CT or CPT with counselling in improving or maintaining cognitive functions (overall cognition; verbal, figural, and working memory; verbal fluency; attention; planning; and visuo-construction) in healthy older adults **(Study II)**?

ii. Which individuals benefit from CT and CPT?
   a. Do sociodemographic variables, neuropsychological test performance at training entry, and/or genetic variables predict CT success in healthy older adults directly after training **(Study I and Study III)** and at follow-up measurement **(Study III)**?
   b. Do sociodemographic variables, neuropsychological test performance at training entry, and/or genetic variables predict CPT success in healthy older adults directly after training **(Study II)**?

c. Which prognostic factors exist to predict memory training performance of healthy older individuals in the literature and how are they assessed, calculated, and reported **(Study IV)**?

## 2. Overview of scientific contributions

In the following, principal information about the scientific contributions in this thesis and their publication are provided (Table 2). Furthermore, an overview of the individual scientific contributions of the doctoral candidate and the co-authors is presented (Table 3).

Table 2: Principal information about the scientific contributions in this cumulative thesis

| | Title | Authors | Journal | Publication state |
|---|---|---|---|---|
| Study I | Structured Cognitive Training Yields Best Results in Healthy Older Individuals, and Their ApoE4 State and Baseline Cognitive Level Predict Training Benefits | **Roheger, M.**<br>Kessler, J.<br>Kalbe, E. | Cognitive and Behavioral Neurology<br>doi: 10.1097/WNN.0000000000000195 | Published 2019 |
| Study II | Effects of a Cognitive Training With and Without Additional Physical Activity in Healthy Older Individuals: A Follow-Up 1 Year After a Randomized Controlled Trial | Kalbe, E.<br>**Roheger, M.**<br>Paluszak, K.<br>Meyer, J.<br>Becker, J.<br>Fink, G.R.<br>Kukolja, J.<br>Rahn, A.<br>Szabados, F.<br>Wirth, B.<br>Kessler, J. | Frontiers in Ageing Neuroscience<br>doi: 10.3389/fnagi.2018.00407 | Published 2018 |
| Study III | Predicting short- and long-term cognitive training success in healthy older individuals: who benefits? | **Roheger, M.**<br>Meyer, J.<br>Kessler, J.<br>Kalbe, E. | Ageing, Neuropsychology and Cognition<br>doi: 10.1080/13825585.2019.1617396 | Published 2019 |
| Study IV | Prognostic factors for memory training success in healthy older individuals: A systematic review and outline of statistical challenges | **Roheger, M.**<br>Folkerts, A.K.<br>Krohm, F.<br>Skoetz, N.<br>Kalbe, E. | | Manuscript |

**Study I:** Structured Cognitive Training Yields Best Results in Healthy Older Individuals, and Their ApoE4 State and Baseline Cognitive Level Predict Training Benefits

The first study "Structured Cognitive Training Yields Best Results in Healthy Older Individuals, and Their ApoE4 State and Baseline Cognitive Level Predict Training Benefits" (Roheger, Kessler, & Kalbe, 2019) was submitted on the 29th August 2018 in the journal *Cognitive and Behavioral Neurology* and was accepted on the 17th February 2019 for publication. The doctoral candidate is the first author of this publication and was involved in the data collection, analysis, and interpretation. Furthermore, she wrote the manuscript.

**Study II:** Effects of a Cognitive Training With and Without Additional Physical Activity in Healthy Older Individuals: A Follow-Up 1 Year After a Randomized Controlled Trial

The second study entitled "Effects of a Cognitive Training With and Without Additional Physical Activity in Healthy Older Individuals: A Follow-Up 1 Year After a Randomized Controlled Trial" (Kalbe et al., 2018) was published in the journal *Frontiers in Ageing Neuroscience.* The manuscript was submitted on 3rd August 2018 and was accepted on 18th December 2018. The doctoral candidate is listed as the second author with a shared first authorship. She was primarily involved in the data analysis and interpretation, and wrote the manuscript.

**Study III:** Predicting short- and long-term cognitive training success in healthy older individuals: who benefits?

The third study "Predicting short- and long-term cognitive training success in healthy older individuals: who benefits?" (Roheger, Meyer, Kessler, Kalbe, 2019) was submitted on the 12th December 2018 in the journal *Ageing, Neuropsychology, and Cognition* and got accepted on the 23rd April 2019. The doctoral candidate is the first author of this study and was mainly responsible for the data restructuring, data analysis and interpretation, as well as the preparation of the manuscript.

**Study IV:** Prognostic factors for memory training success in healthy older individuals: A systematic review and outline of statistical challenges

The fourth study entitled "Prognostic factors for memory training success in healthy older individuals: A systematic review and outline of statistical challenges" (Roheger, Folkerts, Krohm, Skoetz, & Kalbe, in preparation) is a systematic review about prognostic factors for memory training success in healthy older individuals. The doctoral candidate is responsible for all relevant steps in conducting the systematic review and meta-analysis (idea & concept, data collection and analysis, data interpretation, writing of the manuscript).

Table 3: Overview of the individual scientific contributions of the doctoral candidate and the co-authors

| | Idea & Concept | Data collection | Data analysis | Data interpretation | Manuscript preparation | Manuscript revision |
|---|---|---|---|---|---|---|
| Study I | Kessler<br>Kalbe | Kalbe | **Roheger** | **Roheger**<br>Kalbe | **Roheger**<br>Kalbe | Kalbe<br>Kessler |
| Study II | Kalbe<br>Meyer<br>Kessler | Meyer<br>Paluszak | **Roheger** | **Roheger**<br>Kalbe | **Roheger**<br>Kalbe | Kalbe<br>Paluszak<br>Meyer<br>Becker<br>Fink<br>Kukolja<br>Rahn<br>Szabados<br>Wirth<br>Kessler |
| Study III | Kalbe<br>Meyer<br>Kessler | Meyer | **Roheger** | **Roheger**<br>Kalbe | **Roheger**<br>Kalbe | Meyer<br>Kalbe<br>Kessler |
| Study IV | **Roheger**<br>Kalbe | **Roheger**<br>Folkerts<br>Krohm | **Roheger** | **Roheger**<br>Kalbe<br>Folkerts<br>Skoetz | **Roheger**<br>Kalbe<br>Folkerts | Folkerts<br>Krohm<br>Skoetz<br>Kalbe |

# 3. Summary of scientific contributions

The four different studies, which form the basis of the present cumulative thesis, are shortly presented in form of an extended abstract and described in the following chapter. The published articles of Study I (Roheger et al., 2019a), Study II (Kalbe et al., 2018), and Study III (Roheger et al., 2019b), as well as the unpublished manuscript of Study IV (Roheger et al., in preparation), are presented in the Appendix.

## 3.1 Study I

Structured Cognitive Training Yields Best Results in Healthy Older Individuals, and Their ApoE4 State and Baseline Cognitive Level Predict Training Benefits

**Background:** Participating in CT is a possible way to maintain or even improve cognitive functions as we age. As already described in chapter 1.2.1 in the present thesis, several systematic reviews and meta-analysis have shown that CT can be effective in improving cognitive functions in healthy older individuals (Kelly et al., 2014; Martin et al., 2011; Papp et al., 2009). However, all CT programs do not have equal success due to different training-related characteristics, such as training length, training intensity, and whether the training is structured or unstructured (Simons et al., 2016). A structured CT program follows a scientifically based and well-structured manual of instruction, in which the structure and specific content of each training session is described in detail (Bahar-Fuchs, Clare, & Woods, 2013). In contrast to that, an unstructured CT program, often referred to as “unspecific brain jogging”, is a type of training program in which cognitive tasks are randomly combined, without a special focus on either a specific cognitive domain or on a specific target group (Simons et al., 2016). Some studies have found that the best CT effects were achieved with a structured training program in both healthy older individuals (Jaeggi et al., 2008) and patients with Parkinson's disease (Petrelli et al., 2014). Yet, these findings are preliminary and need further research.

Another significant but under-investigated factor which influences CT outcomes is the type of older individuals most likely to benefit from or respond best to CT (Fairchild et al., 2013). As already described in chapter 1.3, several variables may have predictive value for cognitive improvement after CT in healthy older individuals, e.g. age (O'Hara et al., 2007), education (Park et al., 2018), carrying the apoE4 allele (Liu et al., 2013), or neuropsychological test performance at study entry (Rosi et al., 2018). However, the data are far from being conclusive and more research is needed.

**Aims:** In view of the current state of knowledge of CT and CT benefits, our study had two main aims. The first aim was to compare the effects of a structured CT that was specifically developed for healthy older individuals with the effects of an unstructured brain jogging program and a passive control group in the cognitive domains verbal memory, attention, and executive functions. Secondly, we aimed at identifying possible predictors for CT success.

**Methods:** A total of 105 healthy older individuals were recruited via brochures and personal contacts in the University Hospital of Cologne to participate in the study. To be included, participants had to be healthy older individuals, aged 50 to 85 years, who were native German speakers. Exclusion criteria were suspected dementia (DemTect $\leq$ 9; Kessler, Calabrese, Kalbe, & Berger, 2000)), suspected depression (Becks Depression Inventory (BDI) II $\geq$ 14; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and/or other neurologic or psychiatric diseases, as well as insufficiently corrected hearing and/or sight. 70 participants were randomly assigned to either the structured CT group ($n$ = 35), using the NEURO*vitalis* training program (Baller, Kalbe, Kaesberg, & Kessler, 2009), or to the unstructured training group ($n$ = 35), using an inhouse-developed training called Mentally Fit. 35 participants were recruited for the passive control group, yet, due to planning difficulties in the daily clinical routine, these participants were not randomized, but matched for age, sex, and education to the participants in the other two groups. Separately, to create a larger database for the analysis of predictors, we recruited an additional *n* = 45 healthy older individuals who had previously received the structured NEURO*vitalis* training, but were not part of the analysis of training effects.

Figure 1 illustrates the study design. After the screening, all participants received a pre-test, where their cognitive state, memory, attention, executive function and depression status were assessed with a neuropsychological test battery. Furthermore, their apoE4 status was assessed. *N* = 70 participants were then randomly assigned to either the structured NEURO*vitalis* training, or the unstructured Mentally Fit training. The control group was matched and received no training.

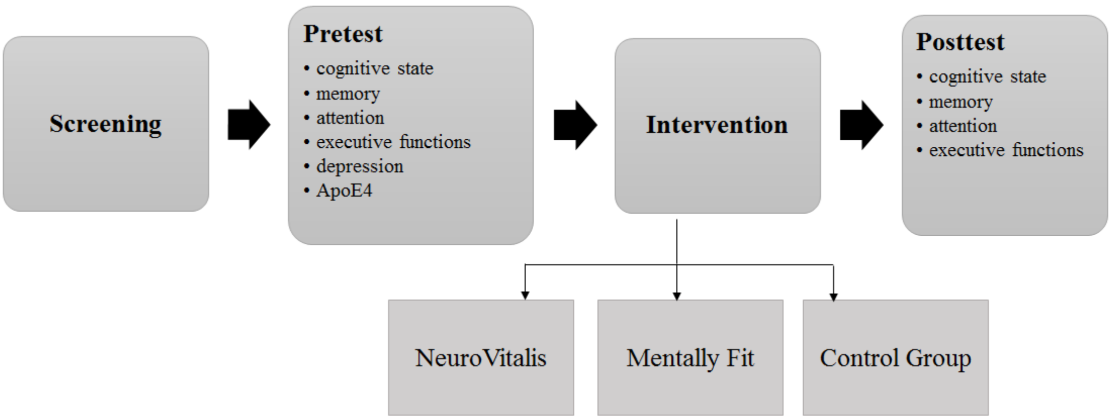


Figure 1: Study design of Study I

Both training programs had the same duration and frequency of training sessions (a total of 12 sessions, each lasting 90 minutes). Participants were trained in small groups of three to eight people. For both training programs, experienced group leaders took responsibility for organizing and carrying out the training. Table 4 gives a detailed overview of the two training programs. At the end of the training, participants were again tested with the neuropsychological test battery, using parallel test versions where available. In the control group, pre- and post-tests were conducted in a parallel interval without training.

Table 4: Overview of Main Characteristics of the two CT Programs Modified According to Petrelli et al., 2015. The inactive control group did not receive any intervention.

| | **Structured program NEURO*vitalis* (NV)** | **Unstructured, not domain-specific program Mentally Fit (MF)** |
|---|---|---|
| **Frequency, intensity** | For both interventions: 12 units at 90 min (twice a week), groups of 3–8 patients | |
| **Training elements** | Psychoeducation<br>Group games<br>Individual tasks<br>Group tasks | Group conversations<br>Group games<br>Individual tasks<br>Group tasks |
| **Main cognitive domains trained** | Attention<br>Memory<br>Executive functions | Attention<br>Memory<br>Executive functions<br>Language<br>Creative thinking |
| **Selection of tasks in specific sessions** | Focused on specific functions (e.g. working memory, planning, and problem solving).<br>If applicable, matched to topic of psychoeducation. | Contains cognitive individual and group tasks that are randomly put together as it is frequently offered in 'memory groups' or 'brain jogging' programs and books; the tasks of the MF program were compiled from a representative choice of tasks of eight frequently used German brain trainings. |
| **Typical session minutes per element may vary between sessions** | 1. Activation games<br>2. Psychoeducation: information about cognitive functions, memory strategies, and other strategies to enhance specific functions, further training possibilities and compensation strategies<br>3. CT in-group setting<br>4. Single cognitive exercises | Combination of group conversations about topics proposed either by the trainer or by the patients themselves (e.g. dealing with the disease, leisure activities) and other elements (order different in the sessions), such as cognitive training in individual or group tasks or a group game. |

To analyse whether the effects of the structured CT NEURO*vitalis* differ from the effects of an unstructured brain jogging program and a passive control group, we used a 2 (Time: Pre- vs. Post-test) x 3 (Training: NEURO*vitalis* vs. Mentally Fit vs. Control group) ANOVA for repeated measures for the cognitive domains verbal memory, attention, and executive functions. To analyse predictors of cognitive improvement after a structured CT, we used backward multiple regressions, using the change score (Δpost-pre) of each domain as the dependent variable, respectively. The predictors age, sex, education, and neuropsychological test performance at study entry were integrated in all regressions. For apoE4 subgroup analysis, t-tests were calculated to compare the change scores (Δpost-pre) between carries and non-carriers of apoE4 for all outcomes, as the total sample size of participants who provided their apoE4 status was too small.

**Results:** The three investigated groups did not differ at baseline in age, sex, education or cognitive status. Significant interaction effects of Time x Training were found in favor of the NEURO*vitalis* group only for the domain verbal short-term memory ($F(2,96) = 7.5$, $p = .001$, $\eta^2_p = 0.14$). Further, overall analysis revealed significant within-subject effects of time for verbal short-term memory ($F(1,66) = 10.04$, $p = .002$, $\eta^2_p = 0.10$), as well as significant between-subject effects of training for verbal short-term memory ($F(2,96) = 8.65$, $p < .001$, $\eta^2_p = 0.15$) and attention ($F(2,87) = 5.39$, $p < .05$, $\eta^2_p = 0.11$). All significant within and between-subject effects were in favor for the NEURO*vitalis* group. No other significant effects were found.

The main results of the predictor analysis were as follows: low neuropsychological test performance at study entry was a predictor for gains in verbal short-term memory ($B = -0.58$), attention ($B = -0.50$), and executive functions ($B = -0.68$). Being female was a predictor for gains in verbal short-term memory ($B = -1.57$) and executive functions ($B = -13.08$). Lower age was a predictor for gains in verbal-long term memory ($B = -0.06$), whereas higher age was a predictor for gains in executive functions ($B = 1.25$). Higher education was a predictor for gains in verbal-short term memory ($B = 0.15$) and attention ($B = 0.12$).

The apoE4 subgroup analysis revealed that non-carriers of apoE4 showed larger differences between pre- and post-training in verbal long-term memory ($t(33) = -2.38$, $p < .05$) and attention ($t(27) = -2,47$, $p < .05$) than carriers, indicating that participants who do not carry the apoE4 allele benefit more from the training.

**Discussion:** The main finding of this study is that healthy older individuals who participated in a structured cognitive training program showed a statistically significant improvement in the domain verbal short-term memory compared to participants of an unstructured training or a control group. This result is in line with various studies which have shown a positive effect of CT on verbal memory (Ball et al., 2002; Chiu et al., 2017) and is of fundamental importance as verbal memory is one of the most vulnerable domain of the normal process of cognitive ageing (Posner, 2011). The fact that the structured training program was beneficial is highly relevant because it demonstrates that the type of training makes a difference. One reason for the beneficial effects of a structured training might be that the structure allows the participants to integrate gained knowledge into established competence more easily. Yet, the full rational for this benefit is still not determined and our study design does not permit clear conclusions, because our training differed in several aspects and not only structure.

Our study further revealed that improvement of cognitive functions after a structured CT can be predicted by neuropsychological test performance at study entry, as well as by the sociodemographic factors age, sex, and education. Low neuropsychological test performance scores at study entry were predictive for improvements. However, it is important to note that our study included a relatively high-functioning sample of older individuals. It is possible that among these participants, the “lower high” can benefit more than the “higher-high” per se. Being female was a predictor for gains in verbal short-term memory and executive functions in the present study. This result supports the assumption of a concept of sex-specific plasticity, that was introduced by Beinhoff et al., (2008). Those authors concluded that the advantage in sex-specific cognitive domains might result in larger plasticity, particularly in verbal episodic memory in women versus visuospatial abilities in men.

The apoE4 subgroup analysis showed that healthy older individuals who were non-carriers of the apoE4 allele benefited significantly more in verbal long-term memory and attention than carriers. Yet, interpretation of our results must take into account the small sample size and future studies are needed to confirm this preliminary data.

Some limitations have to be considered when interpreting the results of the study. First, the clinical trial was not registered. Further, only a part of the study was randomized due to planning difficulties, even though our three groups did not differ regarding sociodemographic variables. Another limitation is the fact that the two trainings used in the study did not only differ in structure, but also in elements that were added to the cognitive task (e.g. psychoeducation). Furthermore, our study had a relatively small sample size; however, the power for a medium interaction effect was still 97% and 99% for strong interaction effects. Also, our study does not include follow-up data and we cannot answer questions regarding transferability effects.

Despite these methodological shortcomings, the present study contributes to the previous research on effectiveness in CT by showing that the structured CT has the potential to enhance cognitive functions in healthy older individuals. A particular strength of the study was the use of an active and a passive control group. Also, the facts that training adherence was monitored and that part of the study was randomized are particular strengths. Further, our study identifies predictors for CT success in healthy older individuals which can help to provide CT programs that are matched to specific individuals in terms of, for example, training difficulty to improve the overall effectiveness of CT programs.

## 3.2 Study II

Effects of a Cognitive Training With and Without Additional Physical Activity in Healthy Older Individuals: A Follow-Up 1 Year After a Randomized Controlled Trial

**Background:** As already described in Chapter 1.2.3 of this thesis, it has recently been discussed whether the combination of CT and PT may yield stronger effects on cognitive functions than each single intervention (Desjardins-Crépeau et al., 2016; Law et al., 2014). Yet, a relevant gap of knowledge refers to the lack of follow-up (FU) data in the existing studies of combined CPT. Zhu et al., (2016) identified only three studies (Linde & Alfermann, 2014; Oswald et al., 2006; Rahe et al., 2015) in their systematic review which investigated long-term effects on CPT, yet all showing moderate effect sizes. Therefore, data seems promising concerning long-term effects of CPT on cognition, but more research is necessary.

In a recent RCT (Rahe et al., 2015), we further studied the effect of CT, CPT and CPT plus additional counseling (CPT+C) on cognitive benefits in healthy older individuals. Results indicated that there was no evidence that CPT was superior to CT. However, there was a significant interaction effect in favor of the CPT+C group in comparison to the CPT group in two executive tasks. Counseling may have trained especially cognitive training strategies and planning abilities. To the best knowledge of the authors, long-term effects of CPT+C in comparison to CPT and CT have not yet been studied.

There is still lacking evidence on possible predictors for CPT in healthy older individuals. However, as already discussed in chapter 1.3.1 of this thesis, there are several variables that may have predictive value for CPT success, among these sociodemographic variables, training variables, genetic variables and neurotrophic growth factors. So far, data is inconclusive and more research is needed.

**Aims:** The aims of the present study, which is based on the RCT by Rahe et al., (2015), but additionally uses 1 year follow-up data are (i) to compare the effectiveness of CT, CPT, and CPT+C training on cognitive functions in healthy older individuals 1 year after the intervention and (ii) to explore predictors of cognitive improvement within the CPT group 1 year after the intervention.

**Methods:** The present study is a multicenter, single-blind RCT, which was registered at the WHO ICTRP (ID: DRKS00005194). Inclusion criteria were age between 50 and 85 years, normal or corrected-to-normal vision and hearing, and German as the native language. Participants were excluded in case of any past or present psychiatric or neurological diseases, a condition that prohibited moderate physical activity, former participation in CT, cognitive impairment (DemTect ≤ 12 points; Kessler et al., 2000), and presence of clinically relevant depressive symptoms (BDI II > 19 points; Beck et al., 1961). *N* = 81 healthy older individuals were recruited and allocated to the three training interventions (CT: *n* = 23, CPT: *n* = 28, CPT+C: *n* = 30).

The three interventions with a maximum of ten participants per group had a frequency of two sessions per week for seven weeks. Each of the 14 sessions lasted 90 minutes. Participants of the CT group received the multi-domain CT NEURO*vitalis* (Baller et al., 2009), which was also contained in the two other interventions. NEURO*vitalis* mainly focuses on the age-sensitive domains memory, attention, and executive functions. Every session is structured and contains single- and group-exercises, activating board games and a short psychoeducational lecture (with topics such as *"Relevance of attentional processes"*, or *"How does memory work?"*). For CPT interventions, the NEURO*vitalis* training was supplemented with a multi-component physical activity program, which took place in the first 20 minutes of each session and followed the guidelines for physical interventions by Nelson et al., (2007). The targeted abilities were strength, flexibility, coordination, and endurance. Further, participants of the CPT had two additional psycho-educational sessions with the contents *"physical activity"* and *"nutrition"*. The CPT+C intervention further included (additional to the NEURO*vitalis* and the physical exercises) motivational counseling. Counseling was performed in the first and the last training week according to the approaches by Marcus & Forsyth, (2009) and Biddle & Mutrie, (1991). It was conducted via two extra appointments with the training: one before the training started to help participants set their goals for the PT, and one after the training finished to check whether the goals were achieved and which strategies or exercises the participants could continue after the training.

Primary outcome measures of the study were performance changes in the domains general cognitive state, memory, attention, executive functions, and visuo-construction. All primary cognitive outcome measures were assessed with an extensive cognitive test battery in standardized, blinded test situations at pre-test, post-test (directly after the training intervention) and at 1-year follow-up. Secondary outcomes were only assessed at pre-test and post-test and could therefore not be integrated in the follow-up analysis. However, they could be used as predictors in the regression analysis. Predictors used in the regression analyses were: physical fitness, peripheral blood levels of BDNF, IGF-1, and VEGF, as well as apoE4 and BDNF polymorphisms.

Groups were analyzed for differences at pre-test using ANOVAs or Chi-square tests as appropriate. Referring to the pre-post comparison of Rahe et al. (2015), we treated the study as two separate trials comparing CPT vs. CT, and CPT vs. CPT+C. 2 (Time: Pre-test vs. follow-up) x 2 (Training: CPT vs. CT / CPT+C vs. CPT) repeated measure ANOVAs were calculated for each primary cognitive outcome measure. In case the assumptions of the ANOVAs were not fulfilled, Friedman's ANOVA was used. Predictors of cognitive improvement after CPT were calculated using backwards multiple regressions. As the dependent variable we used the change score (follow-up – pre-test) of the cognitive variables. The predictors age, education, sex, neuropsychological test performance at study entry, apoE4, BNDF polymorphism, baseline levels of BDNF, IGF-1, and VEGF, as well as overall fitness were integrated into the regression analysis.

**Results:** A total of n = 26 participants dropped out until FU due to health issues, personal reasons and time constraints. However, there were no significant differences between participants and drop-outs of the study in the pre-test demographics, except in the CT group, where participants who dropped out of the study showed a significantly lower score in the DemTect. Further, participants in the three interventions did not differ in their baseline demographic variables at FU.

When comparing CPT vs. CT, no significant *Time x Training* interaction, and no significant between-subjects effect of the factor *Training* could be found. Significant within-subject effects of *Time* were found for the domains verbal short-term memory ($F(1,33) = 12.47$, $p < .01$, $\eta^2_p = 0.27$), figural memory ($F(1,33) = 25.73$, $p < .01$, $\eta^2_p = 0.44$), working memory ($F(1,33) = 15.35$, $p < .01$, $\eta^2_p = 0.32$), and attention, ($F(1,33) = 20.65$, $p < .01$, $\eta^2_p = 0.39$).

Yet, a significant *Time x Training* interaction could be found when comparing CPT vs. CPT + C in the domains general cognitive status ($F(1,36) = 4.94$, $p < .05$, $\eta^2_p = 0.12$), and verbal long-term memory ($F(1,36) = 6.91$, $p < .05$, $\eta^2_p = 0.16$) in favor of the CPT group. Again, no significant between-subjects effect of the factor *Training* could be found. Significant within-subject effects of *Time* were found for the domains verbal short-term memory ($F(1,36) = 7.84$, $p < .05$, $\eta^2_p = 0.18$), figural memory ($F(1,36) = 30.21$, $p < .05$, $\eta^2_p = 0.46$), working memory ($F(1,36) = 12.19$, $p < .01$, $\eta^2_p = 0.25$), verbal fluency ($F(1,36) = 4.75$, $p < .05$, $\eta^2_p = 0.12$), and attention ($F(1,36) = 21.13$, $p < .05$, $\eta^2_p = 0.37$).

The main results of the predictor analyses within the CPT group are: (i) lower baseline performance was a predictor for gains in verbal short-term memory (ß = -.44), verbal fluency (ß = -.59), alternating verbal letter fluency (β = -.40), and attention (ß = -.64), (ii) a lower educational level was a predictor for gains in the domain working memory (ß = -.59), (iii) low blood levels of BDNF were predictive for improvement in alternating letter verbal fluency (ß = -.35) and (iv) higher blood levels of IGF-1 were also predictive for improvement in alternating letter verbal fluency (ß = .36).

**Discussion:** The main finding of the present study is that, even though no significant effects for the comparison CPT vs. CT could be found, significant interaction effects were found when comparing CPT+C vs. CPT, in favor of the CPT group. Furthermore, low cognitive test performance at study entry, low education, low blood baseline levels of BDNF, and high baseline levels of IGF-1 predict, at least in part, an improvement of cognitive functions 1 year after a CPT intervention.

No significant interaction effects favoring CPT in comparison to pure CT could be observed. This result is in line with a meta-analysis from 2016, which also showed no effects for the comparison between CPT and CT (Zhu et al., 2016). Yet, besides the question which training is superior, it should be noted that both trainings, CPT and CT, can be regarded as efficient in stabilizing or even enhancing cognitive functions in healthy older individuals at post-test (Kelly et al., 2014; Law et al., 2014). Our data provide evidence that this is still the case one year after the intervention.

A significant interaction effect was found when comparing CPT+C vs. CPT in favor of the CPT group. We can only speculate about the reasons for this pattern. It may be possible that the higher strains caused by the additional individual counselling sessions in the CPT+C group might have resulted in less training motivation, therefore in less training and consequently in fewer benefits for this group. Accordingly, it may be possible that a concrete training plan without additional individual effort in planning is more appropriate and more efficient for participants who are not highly motivated to individualize their training. In contrast, as “personal training” is an emergent training concept, it can be presumed that there are individuals for who CPT+C will be suitable and even more efficient than CPT. Future research is needed to elaborate on this topic.

Our study showed that lower initial baseline performance predicted gains in the domains verbal short-term memory, executive functions, and attention. This finding is also consistent with several studies showing that lower initial baseline performance is predictive of cognitive training improvement in healthy older individuals  (Rahe et al., 2015; Whitlock et al., 2012). However, also contradictory results exist (Fairchild et al., 2013), showing that participants with an initially higher baseline benefit most from CT. Furthermore, low education, low blood baseline levels of BDNF, and high baseline levels of IGF-1 predict an improvement of cognitive functions 1 year after a CPT intervention. However, it is important to consider the different statistical analyses used and to differentiate between the prediction of short- and long-term effects when interpreting the different patterns of results (e.g., use of backwards or forward multiple regression, latent growth models, etc.), which has not been systematically conducted yet. Overall, the identification of predictors of cognitive interventions gains increasing interest to elucidate the question of who will benefit from CT or CPT interventions to optimize interventions for specific target groups in the future.

Some limitations have to be considered when interpreting our data. First, our study had a small initial sample size and several dropouts to the FU measurement, which reduced the power of the study. Furthermore, our sample was highly educated and our eligibility criteria may have limited the variability of our sample, which would have been necessary to reliable detect predictors of CPT success. Notably, in the CT group, the six individuals that dropped out before the FU, had a significantly lower DemTect score at baseline. Reasons for their refusal to participate in the FU can only be speculated, but it is possible that these individuals had developed cognitive decline, and might have been demotivated to participate in the FU. However, this aspect needs further research. Also, a passive control group was not included in the original study so that cognitive improvements induced by any of our training types can only be estimated in a limited way.

However, a particular strength of the study is the fact it is one of the first that investigates the long-term effects of CT vs. CPT training and therefore adds to the existing literature. The results of future RCTs with long-term data assessment on single and combined cognitive training will have to shed further light on the underlying mechanisms of nonpharmacological interventions to stabilize cognition.

## 3.3 Study III

Predicting short- and long-term cognitive training success in healthy older individuals: who benefits?

**Background:** CT has shown to be effective in improving various cognitive domains in healthy individuals, but as outlined in chapter 1.3 of the present thesis, data is rare and inconsistent regarding the question which specific characteristics of participants predict success of CT. Several variables are under discussion to be predictors for CT success, among them sociodemographic factors (e.g. age, sex, education), cognitive abilities at the entry of training (e.g. baseline performance, general cognition), genetic parameters (apoE-4), and blood factors IGF-1, BDNF, and VEGF. However, this important topic needs to be studied in more detail, as the underlying mechanisms are still a topic of debate and also only few studies investigated short- and long-term predictors of CT success.

**Aims:** The present study aims at identifying possible predictors of CT success directly after a 7-week structured CT (short-term prediction), as well as at one-year FU measurement (long-term prediction). For this purpose, data of an already published RCT were used (Kalbe et al., 2018; Rahe et al., 2015). In those studies, only predictors for short- and long-term effects of CPT were reported, whereas, in the present study, we report upon predictors of short-and long-term effects of CT.

**Methods:** Data were derived from a RCT, which investigated effects of CPT compared with CT and CPT+C and of which follow-up data was presented in Study II in the present thesis (Kalbe et al., 2018; Rahe et al., 2015). In the original study, 20 healthy older individuals (mean age = 67.65 [6.86], ♀ = 12) were trained with CT in Vechta and Cologne, Germany between October 2012 and October 2013. Participants were trained with the CT NEURO*vitalis* (Baller et al., 2009) twice weekly for seven weeks. For a detailed description of the used training and the overall design of the study refer to the Method section of Study II presented in this thesis. We evaluated cognitive changes in the domains of memory, attention, executive functions, visuo-construction, and general cognitive status with an extensive neuropsychological test battery at pre- and posttest and at one-year FU. Assessors were blinded for training group allocation of the participants and had been trained in test application and scoring.

The predictors age, education, sex, baseline cognitive scores, apoE-4, baseline levels of BDNF, IGF-1, and VEGF, and baseline overall fitness were assessed. The predictors age, education (recorded as sum of years at school and further education, e.g., university), and sex (binary: male/female) were recorded before training. For all tests used as outcome measures, the baseline performance scores were included as possible predictors (meaning that, for example, for the outcome "improvement in long-term memory", the predictor "baseline long-term memory status" was included, for the outcome "improvement in general cognition", the predictor "baseline general cognition status" was included, etc.). ApoE-4 status was integrated as a binary variable (Carrier of apoE-4/Non-carrier of apoE-4).

We calculated predictions of cognitive improvement for the CT group at two different time points: at pre-post measurement and at pre-FU measurement. One important issue to consider in training studies is how to measure training gain (Lange et al., 2016): while taking absolute scores, that is the post-test scores (performance after training) as dependent variables in the regression, which would answer the question: "Is x a likely cause of y", we decided to take change scores as the dependent variable, which answers our main question “whose score is most likely to increase/decrease over time?” (Lord, 1967). Change scores are suitable as a way of measuring change, even though they do not take into account differences in relative improvement across persons (Curran-Everett, 2013). Therefore, predictors of cognitive improvement were calculated using backwards multiple regressions using the change scores (analysis 1: post-pre; analysis 2: FU-pre) of cognitive variables as dependent variables for the regression analyses. The predictors age, education, sex, baseline cognitive scores, apoE-4, baseline levels of BDNF, IGF-1,and VEGF, and baseline overall fitness were integrated into the model. Correlations between all predictor variables and the different outcomes (general cognitive state, verbal short- and long-term memory, figural memory, working memory, letter verbal fluency, alternating letter verbal fluency, inhibition, attention, planning, and visuo-construction) were calculated. Variables that had a significant correlation with the outcome variable were integrated into the regression model (assuming a maximum of four predictors per model, due to $n = 20$ in the pre-post prediction and $n = 17$ in the pre-FU prediction). If there were more than four significant correlations between predictors and a specific outcome, the four predictors with the strongest correlations were integrated into the model).

**Results:** Results showed that at pre-post comparison (i) lower baseline performance was a predictor for gains in the domains general cognitive state (ß = −.68), verbal short-term memory (ß = −.66), verbal long-term memory (ß = −.43), figural memory (ß = −.54), working memory (ß = −.48), letter verbal fluency (ß = −.43), inhibition (ß = −.48), attention (ß = −.64), and visuo-construction (ß = −.43), (ii) a lower educational level was a predictor for gains in alternating letter verbal fluency (ß = −.42), (iii) low blood levels of VEGF were predictive for improvement in visuo-construction (ß = −.36), being male was predictive for improvements in figural memory (ß = −.38) and planning (ß = −.45), and (iv) lower scores in baseline physical fitness were predictive for improvement in alternating letter verbal fluency (ß = −.48).

The results of the predictor analyses at pre-FU comparison are (i) lower baseline performance was a predictor for gains in the domains general cognitive state (ß = −.57), verbal long-term memory (ß = −.50), letter verbal fluency (ß= −.68), inhibition (ß = −.57), and attention (ß = −.86), (ii) being male was predictive for improvement in figural memory (ß = −.60), (iii) higher blood levels of IGF-1 were predictive for improvement in working memory (ß = .56), whereas (iv) lower blood levels of IGF-1were predictive for gains in alternating letter verbal fluency (ß = −.41), (v) not carrying the apoE-4 allele was a predictor for improvement in alternating letter verbal fluency (ß = −.42), and (vi) higher blood levels of VEGF were predictive for planning (ß = .57). Table 2 gives an overview of the results of the prediction analysis.

Table 5: Significant predictors of short-term and long-term prediction of CT success, a summary of the results of Study III

| Predictors | Short-term Prediction (7 weeks)<br>*n* = 20 | Long-term Prediction (1 year)<br>*n* = 17 |
|---|---|---|
| Sociodemographic data | | |
| Age | - | - |
| Sex | Being male:<br>- figural memory ↑<br>- planning ↑ | Being male:<br>- figural memory ↑ |
| Education | Lower educational level:<br>- alternating letter verbal fluency ↑ | - |
| Cognitive baseline performance | Lower baseline performance:<br>- general cognitive state ↑<br>- verbal short-term memory ↑<br>- verbal long-term memory ↑<br>- letter verbal fluency ↑<br>- attention ↑<br>- inhibition ↑<br>- figural & working memory ↑ | Lower baseline performance:<br>- general cognitive state ↑<br>- verbal long-term memory ↑<br>-<br>- Letter verbal fluency ↑<br>- attention ↑<br>- inhibition ↑ |
| Physical fitness at baseline | Lower scores in physical fitness:<br>- alternating letter verbal fluency ↑ | - |
| Genetics | | |
| ApoE4 allele | - | Not carrying the ApoE4 allele:<br>- alternating letter verbal fluency ↑ |
| Blood levels at baseline | | |
| IGF-1 | - | Higher blood levels of IGF-1:<br>- working memory ↑<br>- alternating letter verbal fluency ↓ |
| VEGF | Low blood levels of VEGF:<br>- visuo-construction ↑ | Low blood levels of VEGF:<br>- planning ↓ |
| BDNF | - | - |

Note. ↑ = the higher the scores of the predictor, the more benefit. ↓ = the lower the scores of the predictor, the more benefit. Abbreviations: apoE4 = apolipoprotein E 4, BDNF = brain derived neurotrophic factor, IGF- 1 = Immune-globulin factor 1, VEGF = Vascular endothelial growth factor.

**Discussion:** The overall aim of the present study was to find predictors for short- and long-term CT success in healthy older individuals. Yet, our results differed according to the investigated domain and regarding the two different time-points.

We could not identify age as a significant predictor, even though several other studies could (Brooks, Friedman, Pearman, Gray, & Yesavage, 1999b; Verhaeghen et al., 1992). This may be due to the fact that the range of the age distribution in our sample was too small to detect effects.

Concerning sex differences, being male was a significant predictor for figural memory gains at short- and at long-term measurement. Yet, figural memory can be seen as a subdomain of visuo-spatial abilities, which can be defined as symbolic, non-linguistic information that can be represented, transformed, generated, and recalled (Linn & Petersen, 1985). This result fits to the notion of sex-specific plasticity (Beinhoff et al., 2008) and to the data by Munro and colleagues (2012) who showed that men outperform women on tests of visuo-construction and visual perception (Munro et al., 2012).

In line with the compensation hypothesis (Lövdén et al., 2012), in the present study, healthy older individuals with a lower educational level, profited in the domain alternating letter verbal fluency at short-term assessment. This account implies that healthy older individuals, who are already functioning at optimal levels, have less room for improvement in CT performance. Lower initial baseline performance was a significant predictor for CT success in healthy elderly in most of the investigated domains (in particular: general cognitive state, verbal short-term memory, verbal long-term memory, verbal fluency, attention, inhibition, figural and working memory at pre-post assessment; general cognitive state, verbal long-term memory, verbal fluency, attention, and inhibition at pre-Fu assessment). As stated in the compensation hypothesis, gains from CT correlate negatively with cognitive ability and the initial performance (Lövdén et al., 2012). This result is also in line with previous findings, showing that participants with a lower initial baseline performance significantly benefit from CT (Langbaum et al., 2009; Whitlock et al., 2012).

Surprisingly, lower scores in overall baseline physical fitness, assessed with the Senior Fitness Test, were predictive for an improvement in the domain alternating verbal letter fluency. The alternating verbal letter fluency is one of the most demanding tasks in our test battery, and might therefore be most sensitive for cognitive changes in healthy older individuals.

Not carrying the apoE 4 was predictive for improvement in the alternating letter verbal fluency at long-term assessment. This result is in line with our previous results (Rahe et al., 2015) that not-carrying the apoE 4 predicted more gains in an alternating letter verbal fluency task after a CPT - again in the most demanding task of our test battery. In accordance with the findings that apoE 4 affects cognition in healthy older individuals (Wisdom et al., 2011), our data thus indicate that it also has an impact on cognitive plasticity induced by a CT.

Some limitations have to be taken into account when interpreting the results of the present study. First, the sample size is quite small (*n* = 20 at pre-test, *n* = 17 at FU). Also, our sample may be biased due to the fact that our sample was highly educated. Furthermore, participants, who dropped out of the study, had a significantly worse cognitive status than participates at FU. Selectivity concerning education and cognitive status appears to be a more general problem that affects most intervention studies of healthy older people, because participating in a study is always voluntary and it can be assumed that volunteers differ, at least in motivation (Oswald et al., 2006; Unverzagt et al., 2009). Therefore, our sample may represent highly motivated and active older individuals.

A particular strength of the present study is that – to the authors' best knowledge – it is one of the first studies (along with the above-mentioned ACTIVE trial, e.g. Rebok et al., 2013) that investigates predictors of short- and long-term CT success in healthy older individuals. Identifying predictors for CT success is of high relevance especially for targeting CTs to individuals; this field should thus gain more attention in future research.

Summarizing, identifying predictors for CT success in healthy older individuals is a highly relevant, but still an under-investigated area of research. The present study tries to provide initial evidence concerning the question who might benefit most from CT directly after a CT intervention and one year later. Lower initial baseline performance was shown to be predictive in most of the domains for improvement. Future studies should use larger, more heterogeneous samples and include psychosocial variables (e.g. personality traits, self-efficacy, motivation) as possible predictors.

## 3.4 Study IV

Prognostic factors for memory training success in healthy older individuals: A systematic review and outline of statistical challenges

**Background:** As already outlined in chapter 1.2 of the present thesis, CT is a promising approach to maintain cognitive functions to ensure an independent, high-value life even in old age (Sandberg et al., 2016). However, one question that remains under-investigated, is: who (with which profile of e.g. sociodemographic, neuropsychological, genetic parameters) benefits from CT? Prognostic factors (in literature also often referred to as “predictors”) for CT intervention success that are under debate are sociodemographic factors, brain imaging parameters, genetic parameters, and blood factors, as well as personality traits, cognitive abilities at the entry of the training, and different training characteristics, e.g. intensity of the trainings (Park et al., 2018). Yet, inconsistent results regarding prognostic factors of training can be seen in nearly every investigated factor throughout the prognostic factor literature for CT benefits so far. Therefore the question arises, why this is the case. Until now, no systematic review exists investigating prognostic factors for cognitive training success in healthy older individuals in general, and memory training in particular to answer this question (Fairchild et al., 2013). We decided to focus on memory training as a special form of CT because memory is a key function that typically decreases in higher age, even in healthy older individuals (Salthouse, 2013) and because we wanted to ensure a detailed methodological focus of the review.

**Aims:** The main goal of the systematic review is to investigate prognostic factors for memory training success in healthy older individuals. Based on the checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies (Debray et al., 2017; Riley et al., 2019), which can also be used to assess prognostic factors studies, we defined our systematic review question using the PICOTS (Participants, Intervention, Comparator, Outcome, Timing, Setting) system. Our target populations are healthy older individuals, defined as individuals aged ≥ 55 years without any neurological or psychiatric disease (P). We investigated all prognostic factors assessed for memory training success (I). No comparator factor is being considered (C). Outcome events for this review are improvements after memory training in the domains verbal short-term memory, verbal long-term memory, as well as non-verbal short- and long-term memory operationalized with objective and standardized measurement instruments (O). The measurement of the prognostic factor had to be conducted before the start of the memory training and all follow-up information on the outcomes (all time periods) were extracted from the studies (T). Finally, prognostic factor measurement was studied in non-clinical settings (cognitively unimpaired community-dwelling people, as well as cognitively healthy persons in (semi-) residential care) to provide prognostic information for prevention possibilities in cognitively intact individuals (S).

**3.4.3 Methods:** The systematic review was preregistered, the review protocol can be assessed at www.prospero.com (ID: CRD42019127479).

The literature search was conducted in MEDLINE Ovid, Web of Science Core Collection, CENTRAL and PsycInfo up to October 2018. Titles and abstracts were screened according to predefined eligibility criteria by two individual review authors (MR and AKF). Afterwards, the full-text articles of the studies meeting the inclusion criteria were further reviewed for inclusion in the systematic review. In cases where no consensus could be reached between the two authors MR and AKF, a third author (NS) was asked and the case was discussed until a final consensus was reached.

The review included peer-reviewed studies in English and German with no limitations regarding publication date which investigated prognostic factors of memory training success. A prognostic factor is defined as any measure that, among people with a given condition (process of ageing, the start point), is associated with a subsequent outcome (an endpoint, worsening of cognition; Riley et al., 2013). Full study reports needed to be available; abstracts, books, book chapters, study protocols, and conference papers were excluded. Prognostic factor studies on healthy older participants (age ≥ 55 years) were included. All prognostic factors (e.g. sociodemographic factors, brain imaging parameters, genetic parameters, blood factors, personality traits, cognitive abilities at the entry of the training, different training characteristics, e.g. intensity of the trainings, etc.) which investigate effects of memory training were included in the review and meta-analysis. Memory training was defined as a CT that primarily targets on memory performance with a minimum of two sessions in total. The memory training can either include computerized or paper-pencil tasks with clear cognitive rationale, which are administered either on personal devices or in individual- or group settings. When multi-domain approaches were examined, memory had to be the main component of the program (at least 50% of the exercises). Factor studies, which investigate memory training benefits as an outcome (verbal or non-verbal short- or long- term memory) measured with established objective neuropsychological tests, were included.

Two review authors (MR and AKF) independently extracted the data according to the Critical appraisal and data extraction for systematic reviews of prediction modelling studies_ prognostic factors (CHARMS_PF) checklist (Moons et al., 2014) to investigate the reporting of prognostic factors, a standardized data extraction form was used.

Two reviewers (MR and AKF) independently assessed the extracted studies for the risk of bias using the Quality in Prognosis Studies (QUIPS) checklist, developed by Hayden and colleagues (2013) to examine the risk of bias in prognostic factors studies across six domains (Hayden, van der Windt, Cartwright, Côté, & Bombardier, 2013): Study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other prognostic factors, statistical analyses and reporting. Each of the six domains was judged with high, medium or low risk.

In the pre-registration of the study, we registered a meta-analysis to investigate the predictive performance of the different prognostic factors. However, after data extraction, we found that data on prognostic factors after memory training were too heterogonous and too poorly reported to conduct a meta-analysis.

**Results:** 10,703 studies were identified through the database search. After removing the duplicates, 8,218 studies were screened. It was difficult to distinguish between prognostic factor finding studies and model development studies from study abstracts alone. Thus, we assessed 797 full-texts for eligibility. Finally, *n* = 28 studies were included in the present review.

The investigated samples were, with only five exceptions, highly educated throughout the studies, ranging from a mean of 11.9 years to a mean of 18.77 years of education. The MMSE ranges from a mean of 25.9 points to 29.17 points. In most studies, the samples consisted of more women than men, with an overall of 65.9% women and 34.1% men participating in the studies. Many different types of memory trainings were used including the training of the Method of Loci, psychoeducation about memory processes, and learning and practicing different memory strategies. The total length of the training sessions varied from 240 minutes to 2700 minutes.

We investigated four outcomes: verbal short-term memory, verbal long-term memory, non-verbal short-term memory, and non-verbal long-term memory. 21 of 28 studies investigated verbal short-term memory as an outcome, 11 of 28 studies investigated verbal long-term memory, only two out of 28 studies investigated non-verbal short-term memory, and four studies investigated non-verbal long-term memory as an outcome. There was a huge heterogeneity in the statistical outcome measures used. In total, eight studies used the post-test scores as the dependent variable for their calculations, whereas 18 studies used the change score (defined as Δpost-pre scores) as the dependent variable for their prognostic factor calculation. Residual change scores, which are standardized residuals from linear regressions of post-test scores on pre-test scores to provide a simple change score adjusted for baseline variance (Prochaska, Velicer, Nigg, & Prochaska, 2008), were used as the dependent variable in only four studies.

There was no detailed description (e.g. a separate paragraph stating not only the name of the predictor and method of measurement, but also blinding, and use in the statistical analysis (e.g. as a continuous or dichotomous factor)) of the candidate predictors in most of the studies, probably as a consequence of the fact that the prediction analysis was mostly not the primary goal of the investigated articles. Investigated predictors include sociodemographic variables (age, sex, education, and ethnicity), neuropsychological test status at study entry in different domains, imaging measures, training characteristics, genetic variables (apoE4) and personality traits. There were several different statistical methods used to calculate the impact of prognostic factors after memory training on memory outcomes. Eight studies calculated a multiple regression, two studies used a mixed model approach, and 12 studies used correlation analysis to investigate prognostic factors.

One of the overall aims of the present systematic review was to systematize which prognostic factors are predictive for which of the four investigated memory outcomes. There is a similar pattern that can be detected over all four outcome domains: the direction of the prognostic factor (the more of x/ the less of x) is dependent on the used dependent outcome measure. This finding is substantial for the interpretation of the current literature on prognostic factors of memory training success in healthy older individuals. In the domains verbal short-term and verbal long-term memory younger age was a predictor for improvement, but only in studies using the post-test score as a dependent variable. Studies which use change scores as the dependent variable to predict the influence of age on memory improvement in verbal short-term and verbal-long term memory show that higher age was predictive for memory improvement.

Regarding the reporting quality, important information is lacking throughout the investigated studies, especially regarding the domains study attrition, prognostic factor measurement, study confounding and statistical analysis and reporting. Therefore, the studies in their entirety were difficult to comprehend.

**Discussion:** This is the first systematic review that examines prognostic factors of memory training success on memory in healthy older individuals. The most important result is that the tendency of the prognostic factor (the more of x/ the less of x) is conditional on the used dependent outcome measure (post-test scores vs. change scores vs. residual scores). This finding is substantial for the interpretation of the current literature on prognostic factors of memory training success in healthy older individuals. Until now, it was unclear, why the directions of prognostic factors differed across studies. So far, many possible explanations regarding characteristics of the used memory training, measurement procedures and the investigated sample existed (Roheger, Meyer, Kessler, & Kalbe, 2019; Sandberg et al., 2016). The present systematic review suggests, however, that these heterogeneous findings can be explained by the different statistical methods used for prediction analysis so far, especially the different dependent outcome measures (post-test scores vs. change scores vs. residual scores). It is important to consider that the different dependent variables can theoretically answer different questions: while taking absolute scores, that is the post-test scores (performance after training) as dependent variables in the regression answers the question “Is x a likely cause of y”, taking change scores as the dependent variable answers the question “whose score is most likely to increase/decrease over time?” (Lord, 1967). Yet, this distinction is also essential for clinical decision processes in order to decide which training is best suited for a specific individual. Therefore, when reading and interpreting prognostic factor data of memory training improvement, our systematic review shows that it is of outstanding importance to take a closer look on the dependent variable used to measure training improvement.

The only predictor that has been measured in several of the studies investigating verbal short- and long-term memory is “age”. In studies which used the post-test score as the dependent variable, participants with younger age showed higher scores after the memory training intervention, whereas when using the change score, older participants benefited most. The latter result can be interpreted with the compensation hypothesis, stating that older participants have more room for improvement. When we want to investigate which participants benefit (using change scores as the dependent variable), it seems that older participants can benefit more due to the fact that they may have more room for cognitive improvement according to the compensation hypothesis (Lövdén et al., 2012). This account implies that healthy older individuals who are already functioning at optimal levels have less room for improvement in memory training performance. When we look on the post-test performance, it is logical that younger participants then perform also better after the training.

Further investigated predictors include sociodemographic factors (as sex, education, ethnicity), neuropsychological test status at study entry in different domains, imaging measures, training characteristics, genetic variables (apoE4), and personality traits.

Our systematic review shows that the included studies not only used different dependent variables, but also different statistical methods to calculate prognostic factors: e.g. linear regression models, correlation analyses, mixed models, and group comparisons. However, not all used methods are suitable to answer the question of who benefits most from memory training.

When interpreting the results of this review, there are a few more limitations that have to be taken into account. First, it was difficult for the authors to distinguish between prognostic factor and prognostic model studies, as the reporting was fairly poor in most studies. Most studies did not state whether their aim was to investigate a factor (the influence of one prognostic variable on the outcome), or a model (the influence of two or more prognostic variables and their interactions on the outcome). Further, the statistical methods were not clearly reported so that in some cases it was not possible to determine which prognostic variables were used in the final calculations. Therefore, a clear distinction may not have happened in all included studies.

Furthermore, there was no scoring system regarding the assessment of the risk of bias tool QUIPS (Hayden et al., 2013) to standardize the risk of bias assessment over other systematic reviews. As a final limitation, the present systematic review only focuses on memory outcomes after memory training, hereby disregarding all other cognitive domains, as well as other outcomes (e.g. depression, quality of life, instrumental activities of daily living), and broader cognitive training interventions in general. The authors decided to use memory as it is a key function in the ageing process and to get a first overview over the published data on prognostic research after training interventions in a narrower frame. Yet, the gotten results and conclusions regarding the statistical analysis of the prognostic factors of memory training success might also be transferred to other trainings and cognitive outcomes. As a clear recommendation, independent of the investigated nonpharmacological intervention and the investigated outcome, one should be aware of the used dependent variable and statistical methods to assess prognostic factors. We recommend the use of the change score as a dependent variable to answer the question “who benefits” from a nonpharmacological intervention and to use multiple regression analysis or structural equation models instead of correlation analysis and group comparisons.

Summarized, this systematic review on prognostic factors of memory improvement after memory training shows huge short-comings in methodological reporting and statistical analyses. Thus, the need of elaborated prognostic factor studies with huge sample sizes, clear descriptions of prognostic factor and confounder measurement, and clear reporting standards are emphasized. Furthermore, a special focus on the use of the dependent variables used for prognostic factor calculation should clearly be established. Prognostic factor research should not be an “add-on” to already existing studies, but should be a separate focus following clear reporting and conduction guidelines, as prognostic factor research is of high importance for aiding treatment and lifestyle decisions, improving individual dementia risk prediction, and providing new treatment options (Riley et al., 2013).

# 4. Discussion

The main goals of the present cumulative thesis were (i) to examine whether CT and CPT are effective in improving or maintaining cognitive functions in healthy older adults (Study I and Study II), and (ii) to investigate which individuals benefit from CT and CPT (Study I, Study II, Study III, Study IV). In more detail, it was investigated whether a structured CT intervention was more effective than an unstructured brain jogging program and a passive control group (Study I), and whether a CPT may be more effective than a pure CT or a CPT with counselling (Study II). Furthermore, (iii) possible predictors for CT training success (Study I and Study III), as well as for CPT training success, were identified (Study II); and (iv) in an attempt to systematize the current research on predictors of CT success, a systematic review of the literature was conducted to identify which prognostic factors exist to predict memory training performance of healthy older adults and how they are assessed, calculated, and reported (Study IV).

Following, these research questions are discussed by concatenating the four studies of the cumulative thesis and thereby discussing the additional research benefit of these scientific contributions to the current state of research. General limitations, as well as strengths of the contributions, are presented and discussed and further research implications, and also implication for daily life, are highlighted. The thesis closes with a short conclusion.

## 4.1 Effectiveness of CT and CPT in healthy older adults

The effectiveness of CT and CPT interventions in healthy older individuals was investigated in Study I and Study II of the present thesis. Study I investigated whether participation in structured CT was more effective than participation in an unstructured brain jogging program or a passive control group. Results indicated that significant interaction effects of *Time x Training* were found in favour of the structured CT group for the domain verbal short-term memory. Furthermore, on a descriptive level, a clear trend in favour of the structured CT program was demonstrated in the domain of attention. The fact that the structured CT program was beneficial for our study participants is highly relevant for prevention of cognitive ageing, because it demonstrates that the type of training participants experienced makes a difference. The structure of the training programs seems to be a crucial feature on which the benefits depended. This result is in line with the findings of Jaeggi et al. (2008), who showed that the best effects were achieved using a structured working memory training program in a sample of healthy participants (Jaeggi et al., 2008), and of Petrelli et al. (2014), who showed that only a scientifically based, structured training program was beneficial for enhancing cognition compared with unspecific brain jogging and a waitlist control group in a sample of non-demented patients with Parkinson’s disease (Petrelli et al., 2014). Therefore, the present thesis can add to the previous literature by showing that among other factors influencing training effectiveness, such as, for example, participants’ motivation and alertness (Boot, Simons, Stothart, & Stutts, 2013; Duckworth, Quinn, Lynam, Loeber, & Stouthamer-Loeber, 2011), and training duration (Lauenroth et al., 2016), the structure of the training used plays an important rule for benefits in the trained domains in healthy older adults. Therefore, healthy older adults also should be wary of using unscientific, unstructured “brain-trainings”, which are sold by companies and promise enhancement of cognitive plasticity, and rely instead on scientifically based, structured training programs.

Study II investigated whether CPT may be more effective than pure CT or CPT with counselling one year after the intervention. We showed a significant *Time x Training* interaction favouring CPT in comparison with CPT plus counselling in the domains overall cognition and verbal long-term memory. Also, within-group comparisons showed cognitive improvements for all types of training. In the previous literature, it has been proposed that CPT interventions might induce larger functional benefits on cognition in healthy older adults than each type of intervention on its own (Hötting & Röder, 2013; Kraft, 2012). So far, CPT studies that were conducted in healthy older adults have shown mixed results (Desjardins-

Crépeau et al., 2016). Studies exist that show evidence for significant benefits of CPT over single domain training (Fabre et al., 2002; Oswald et al., 2006). However, contradictory results exist also demonstrating no additional cognitive enhancement after CPT when compared with CT alone (Shatil, 2013).

The question whether CPT is more favourable for cognitive improvement compared with pure CT cannot therefore be answered conclusively, even though our data support the notion that both trainings yield comparable results. However, even though CT (Kelly et al., 2014), PT (Erickson et al., 2013), and CPT (Law et al., 2014) show positive effects on cognition in healthy older adults, only physical activity shows positive effects on cardiovascular risk factors, which, in turn have a negative effect on cognitive abilities in more advanced age (Fillit, Nash, Rundek, & Zuckerman, 2008). Therefore, it might be possible that CPT is even more promising for maintaining and improving cognitive functions in more advanced age. A network-meta-analysis comparing all RCTs on CT, PT, CPT, and control groups is needed, however, to give a proper answer to the question which training is more promising in improving cognition in the long-term.[3] Furthermore, it may be promising to systematically investigate activities such as dancing (Kattenstroth, Kalisch, Holt, Tegenthoff, & Dinse, 2013), juggling (Boyke, Driemeyer, Gaser, Büchel, & May, 2008), or tai-chi (Mortimer et al., 2012) as CPT interventions, because these types of activities also combine cognitive and physical aspects and are easier to integrate into everyday lives than planned group interventions. Overall, research on these nonpharmacological interventions is highly important to offer a safe intervention without side effects with the overall goal to maintain and improve cognitive functions in healthy older adults so that greater independence and a better quality of life can be maintained until old age.

[3] It should be noted that our department already wrote a grant application to the German Ministry of Education and Research to conduct a systematic review and network meta-analysis on the comparison of the efficacy of CT, PT, and CPT compared with a passive control group.

Long-term effects are the ultimate goal for interventions on cognition in healthy older adults, as these effects promise more independence and better cognitive functioning with healthy ageing. Notably, there is a lack of knowledge on follow-up data especially on CPT intervention success. Zhu and colleagues (2016) could only identify three studies in their meta-analysis investigating the cognitive effects of CPT (Zhu et al., 2016). Yet, the results of the present thesis could add to the current knowledge and show that CPT is also effective one year after the conducted intervention.

In general, critics of CT and CPT interventions raise concerns due to the heterogeneity of the conducted trainings (e.g., paper-and-pencil vs. computerized; single- vs. multi-domain; different foci), the variability in lengths and settings (at home vs. community settings), and the diversity of the population studied (Bahar-Fuchs, Martyr, Goh, Sabates, & Clare, 2019). However, an important distinction, which is mostly ignored in studies, is the difference between clinical and theoretical goals and - in most cases - design of a CT or CPT study cannot optimize both (Jacoby & Ahissar, 2013). On the one hand, it is important to conduct well-designed and controlled CT or CPT with a relatively homogeneous sample to investigate and understand the underlying mechanisms of the trainings. On the other hand, CT and CPT that can be easily implemented in everyday life with heterogeneous samples, which reflect the everyday and also clinical routine, are of high importance to design and provide helpful prevention approaches.

To summarize, designing effective interventions to enhance cognition is promising and has enormous potential, with applications ranging from normal cognitive ageing to dementia and other neuropsychological disorders, but it also provides challenges regarding logistical and methodological shortcomings of RCTs (Moreau, Kirk, & Waldie, 2016). Yet, the present thesis could essentially contribute to the current state of knowledge by showing that a structured CT may be more effective than an unstructured, not scientifically based “brain training”. It could also show that both CT and CPT interventions are helpful to enhance cognition in healthy older adults one year after the intervention and could help to close a gap in the present research on long-term effects, especially on CPT interventions. Thus, the present thesis could show that CT and CPT interventions are a promising prevention approach for healthy older adults to maintain and enhance cognitive functions, not only in the short-, but also in the long term.

As already outlined in the Introduction and in the summaries of the studies conducted, several different types of CTs and CPTs exist, which also target different outcomes. Hence, it is also essential to investigate not only if CTs and CPTs are effective, but also for which individuals these trainings are effective (which specific profile, e.g. age, education, sex) profits most from which type of training) in order to ensure an individual-centered treatment approach.

## 4.2 Predictors of CT and CPT success in healthy older adults

To ensure an individual-centered prevention approach for cognitive decline in older age, the second research aim of the present thesis was to identify which individuals benefit most from CT and CPT. Study I and Study III investigated the question whether sociodemographic variables, neuropsychological test performance at training entry, and/or genetic variables predict CT success in healthy older adults directly after training (Study I and Study III) and at follow-up measurement (Study III). Study II investigated possible predictors for CPT success in healthy older individuals directly after the training. Furthermore, a systematic review was conducted (Study IV) to identify predictive factors for memory training performance (as a special form of CT) in healthy older adults and to assess how these factors are reported and calculated.

The results of short- and long-term predictors of CT success (Study I and Study III) are summarized in Table 6. Regarding short-term predictors of CT success in healthy older adults, both studies show that participants with a lower neuropsychological test performance at training entry could benefit most in nearly all domains investigated. This result is in line with the compensation hypothesis (Lövdén et al., 2012), which posits that participants who are already functioning at optimal levels have less room for improvement in CT performance. Accordingly, participants who start with an initially lower performance will gain more from CT (see also Section 1.3.1 for a more detailed explanation). Therefore, this result is promising for healthy older adults who hesitate to start CT because they are afraid that their performance is already too low - it is possible that they can benefit even more from the CT.

Results regarding education as a predictor for short-term CT success are mixed: in the domains verbal short-term memory (Study I) and attention (Study I), participants with a higher educational level profit more from the training, which is in line with previous literature showing that higher education might be a predictor for memory improvement after 10 weeks of CT (Langbaum et al., 2009). In contrast, in the domain alternating letter verbal fluency (Study III), participants with a lower educational level profit more. Yet the trainings used in both studies are the same in regard to content and length. However, this result might be explained by the fact that the domain alternating verbal letter fluency was assessed with one of the most demanding tasks in the test battery and might thus be most sensitive to changes or gains induced by CT in a population of healthy older adults (Roheger et al., 2019). Further, education might not only represent years of schooling, but can also be seen as a proxy variable for socioeconomic status and other lifestyle factors, early life factors, or motivation for learning (Krieger, Williams, & Moss, 1997; Langbaum et al., 2009).

Also, results regarding age as a predictor for CT success directly after the training are mixed: younger participants benefit most in the domain verbal long-term memory, whereas older participants benefit most in the domain set-shifting. Memory plasticity in general decreases over the adult life span (Baltes, Sowarka, & Kliegl, 1989) and therefore older age might negatively affect gains in CT that specifically target memory.

A further predictor regarding short-term CT benefits in healthy older adults seems to be sex. Study I showed that being female predicts improvements in the domains verbal short-term memory and set-shifting, Study III showed that being male predicts improvements in the domains figural memory and planning. These results fit with the notion of sex-specific plasticity (Beinhoff et al., 2008) and the data of Munro et al. (2012), who showed that male participants outperform female participants on tests of visuo-construction and visual perception, whereas female participants outperform male participants on tests of psychomotor speed and verbal learning and memory (Munro et al., 2012). These differences might be due to sex differences in biological factors such as neuronal lateralization (Gur et al., 2000), areas of relative brain metabolism (Li et al., 2004), region-specific brain dimorphism (Cowell, Allen, Zalatimo, & Denenberg, 1992) and/or circulating hormone levels (Silverman, Kastuk, Choi, & Phillips, 1999). Yet, when investigating sex as a predictor for CT success, it is important to note that sex is usually categorized in a binary manner (as female or male), even though there is variation in the biological attributes that constitute sex and its expression (Heidari, Babor, Castro, Tort, & Curno, 2016).

Regarding predictors of long-term CT success (Study III), similar results were detected: participants with a lower neuropsychological test performance at study entry benefit, and also sex differences can be seen. Further, blood levels of IGF-1 and VEGF showed significant predictive value. IGF-1 is important in adult neurogenesis and therefore also for cognitive functions (Ziegler, Levison, & Wood, 2015) and increased VEGF is associated with improved connectivity between temporal lobe structures (Voss et al., 2013). Further results on blood levels of these factors as predictors for CT success in healthy older adults is lacking and the present thesis is one of the first studies showing that higher blood levels of IGF-1 and VEGF predict training benefits.

Table 6: Significant predictors of short-term and long-term prediction of CT success, a summary of the results of Study I and Study III

| | Cognitive domains | Study I | Study III |
|---|---|---|---|
| Short-term assessment Directly after training | General cognitive state | n.a. | Baseline performance ↓ |
| | Verbal short-term memory | Baseline performance ↓<br>Being female<br>Education ↑ | Baseline performance ↓ |
| | Verbal long-term memory | Baseline performance ↓<br>Age ↓ | Baseline performance ↓ |
| | Figural memory | n.a. | Baseline performance ↓<br>Being male |
| | Working memory | n.a. | Baseline performance ↓ |
| | Letter fluency | n.a. | Baseline performance ↓ |
| | Alternating letter fluency | n.a. | Education ↓<br>Physical Fitness Baseline ↓ |
| | Inhibition | n.a. | Baseline performance ↓ |
| | Attention | Baseline performance ↓<br>Education ↑ | Baseline performance ↓ |
| | Planning | n.a. | Being male |
| | Set-shifting | Baseline performance ↓<br>Being female<br>Age ↑ | n.a. |
| | Visuo-construction | n.a. | Baseline performance ↓<br>VEGF ↓ |
| Long-term assessment 1 year after training | General cognitive state | No long-term assessment conducted in Study I | Baseline performance ↓ |
| | Verbal short-term memory | | / |
| | Verbal long-term memory | | Baseline performance ↓ |
| | Figural Memory | | Being male |
| | Working memory | | IGF-1 ↑ |
| | Letter fluency | | Baseline performance ↓ |
| | Alternating letter fluency | | IGF-1 ↓<br>Not carrying ApoE 4 |
| | Inhibition | | Baseline performance ↓ |
| | Attention | | Baseline performance ↓ |
| | Planning | | VEGF ↑ |
| | Set-shifting | | n.a. |
| | Visuo-construction | | / |

*Note:* n.a. = not assessed in the Study; ↑ = higher scores show improvement in the domain, ↓ = lower scores show improvement in the domain.

Notably, to the author's best knowledge, the present thesis is one of the first that investigates the differences in predictors of short- and long-term CT success (directly after training and one year after training). Yet, this distinction is of high importance to allow choosing the best-fitting nonpharmacological intervention depending on the individuals' goals. The present thesis shows that predictors for short-and long-term CT success seem rather similar, except that in the long term, blood levels seem to become more important predictors, maybe due to the fact that they induce structural changes on a neural level that need a longer period of time to occur and manifest.

Study II investigated possible long-term predictors for CPT success in healthy older individuals one year after the training. Results showed again that lower neuropsychological test performance at study entry was a significant predictor for CPT gains in nearly all domains investigated, a lower education level was predictive for improvements in working memory, lower blood levels of BDNF were predictive for gains in the domain alternating letter verbal fluency, and higher blood levels of IGF-1 were also predictive for improvement in alternating letter verbal fluency. Therefore, the only difference in comparison with predictors for pure CT was the blood levels of BDNF. BDNF is considered to mediate the effects of exercise on synaptogenesis, synaptic plasticity, and enhanced learning and memory (Cotman et al., 2007), which is in line with our results that BDNF was a predictor of CPT success, but not CT success.

As an interim conclusion, it seems that "more vulnerable" groups, meaning individuals who received less education, who are at an older age, and who show worse performance on neuropsychological tests at training entry can benefit more from CT as well as from CPT at both time points: directly after the training and one year after the training. This result is promising as it implies that it is never too late to start to train cognitive abilities in older age, regardless of former experiences. However, it may also imply that there is the need to design CTs and CPTs that are more difficult or even adaptive. This would allow individuals who are already or still functioning at a high cognitive level to be able to profit and to challenge their cognitive abilities. Hence, the results of the present thesis can help in the design of new and more matching interventions to maintain cognitive functions. Therefore, future research should systematically investigate the relationship between different levels of training difficulty and neuropsychological test performance at study entry, either with the use of different groups of training difficulties or with the use of an adaptive CT and/or CPT. Further, when designing new CTs and/or CPTs, special focus should be given to sex differences and to how to design tasks that offer the possibilities for all to improve. Also, as sex is not a binary variable, other methods to measure sex and the distinction between sex and gender in research on healthy older adults in a non-clinical context should be reflected in further research. The present thesis thus contributes to a great extent to a more individualized approach to preventing cognitive decline in older age.

A systematic review was conducted (Study IV) to identify predictive factors of memory training performance (as a special form of CT) in healthy older adults and to assess how these factors are reported and calculated. As there exists a huge amount of different kinds of CTs and several outcomes that can be investigated, which all might be predicted by different factors (see Figure 2 for a schematic overview), we decided to focus the systematic review on memory training and memory outcomes (verbal short- and long-term memory, as well as non-verbal short- and long-term memory). This decision was made because memory is a key function that typically decreases with advancing age, even in healthy older individuals (Salthouse, 2013) and because we wanted to ensure a detailed methodological focus of the review.

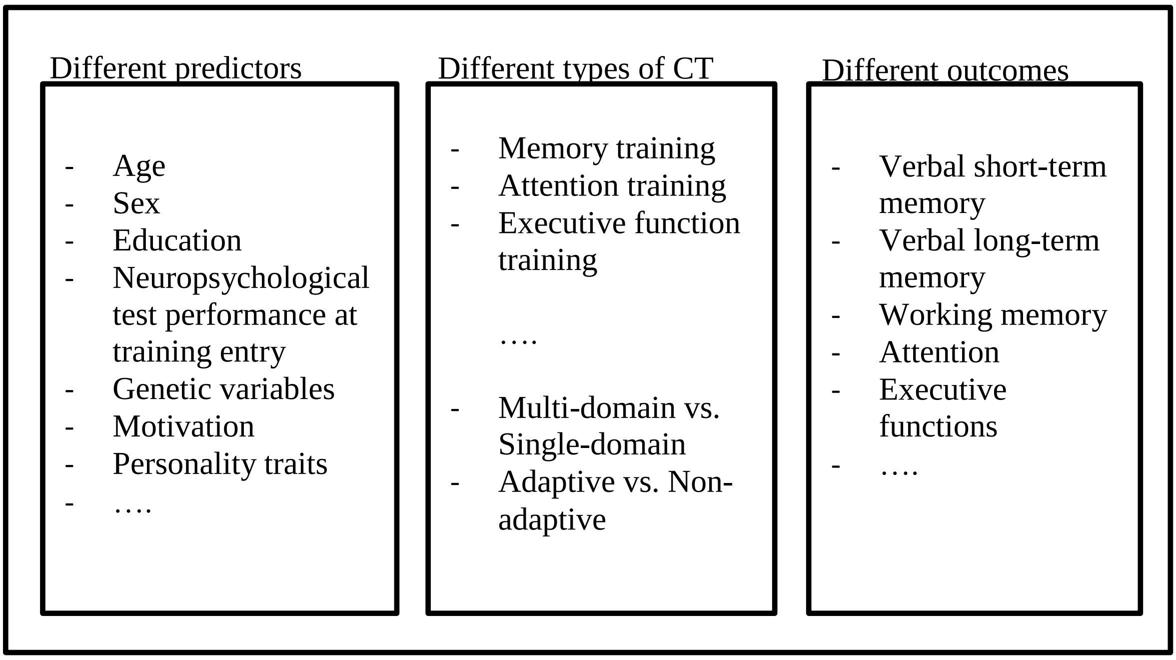


Figure 2: Schematic overview of different predictors, types of CTs, and outcome variables, which have to be considered when investigating predictors of CT

A systematic review of 28 studies was conducted. Results of the review show that a huge number of different predictors was assessed throughout the different studies investigated, yet most of the predictors were not systematically assessed. This may be due to the fact that prognostic factor research is often a study “add-on” or a secondary or tertiary aim of a study instead of the primary aim and thus constitutes an exploratory research approach. Yet, prognostic/prediction research should be a separate focus following clear reporting and design guidelines, as it is of high importance for aiding treatment and lifestyle decisions, improving individual dementia risk prediction, and providing new treatment options (Riley et al., 2013). Assessed predictors throughout the studies were: age, education, sex, neuropsychological test performance at study entry, imaging measures (activity in frontal cortex and hippocampus, hippocampal volume, amplitude of low frequency fluctuation, white matter structure), ethnicity, subjective reported memory, depression, openness for experiences, extraversion, neuroticism, self-rated confidence, activities of daily living, apoE4 status, functional limitations, memory specificity, and characteristics of the conducted training (e.g. frequency and length). Summarized, the significant predictors for memory training success in healthy older individuals throughout the studies show the same pattern as our data from RCT analyses: more advanced age and lower education indicate that more “vulnerable” groups can benefit more from the provided trainings. However, most of the investigated predictors did not significantly contribute to training success.

It could be regarded as an even more important result that the present thesis was the first study to show that the tendency of the prognostic factor (the more of x/ the less of x) is conditional on the dependent outcome measure used (post-test scores vs. change scores vs. residual scores). This finding is substantial for the interpretation of the current literature on prognostic factors of memory training success in healthy older adults and predictors of CT success in general. Until now it has been unclear why the directions of prognostic/predictive factors differed across studies. Thus, many possible explanations regarding characteristics of the memory training used, measurement procedures, and the sample investigated were discussed (Sandberg et al., 2016). The present thesis suggests, however, that these heterogeneous findings can be explained by the different statistical methods used for prediction analyses so far, and the different dependent outcome measures (post-test scores vs. change scores vs. residual scores). It is important to consider that the different dependent variables can theoretically answer different questions: while taking absolute scores, that is the post-test scores (performance after training), as dependent variables in the regression, answers the question "Is x a likely cause of y", taking change scores as the dependent variable answers the question "whose score is most likely to increase/decrease over time?" (Lord, 1967).

We can conclude that when reading and interpreting prognostic factor data on memory training improvement, the present thesis shows that it is of outstanding importance to take a closer look at the dependent variables used to measure training improvement and thus provides a simple yet appealing answer to the question why results on prognostic factor research so far have shown highly inconsistent results. Consequently, further steps to a deeper understanding of prognostic factor research are the investigation of a methodological approach to detect further statistical patterns of the different calculations and dependent variables used, as well as the investigation of a real-life setting approach to test the findings in a population of healthy older individuals engaging in CT.

For the methodological approach, a data simulation was conducted with R in which different samples size ($n$ = 100, 200, 300, 500, 1000) of participants who attended a CT were simulated (meaning that a pre-post design of two groups was simulated, a CT group and a passive control group). The CT group showed significant improvements at post-test measurement, and the control group only showed small retest effects at post-test measurement. The two groups showed a non-significant, comparable performance at pre-test measurement. We then simulated a predictor that had a significant effect on the training improvement and calculated different multiple regression models while systematically including different predictors (e.g. neuropsychological test performance at study entry, group factor) for all three dependent variables we were interested in (post-test scores, changes scores, and residual change scores).[4] For the real-life setting approach, data (*n* = 2,912 healthy older individuals) from an online cognitive training package (Corbett et al., 2015) were analyzed to investigate predictors of online CT success directly after training, and 3 and 6 months after training. The overall aim was to be able to give clear recommendations regarding the best way to calculate predictors of online CT success in healthy older individuals to answer the question: who benefits most from online CT.

To summarize, the results show that more "vulnerable" groups (participants with higher age, lower education, lower neuropsychological test scores at training start) seem to benefit more from the CTs and CPTs conducted so far. Also, sex differences have to be taken into account when investigating predictors for CT and CPT success. Further, the present thesis is one of the first studies that examine predictors of short- and long-term CT and CPT success. Also, we were able to close a research gap in the literature by showing that inconsistent results regarding predictors of CT and CPT success are due to different statistical methods and dependent variables used. As a next step, clear recommendations are needed (and are already in progress) to systemize the assessment of predictors of CT and/or CPT performance to ensure a more individual-centered prevention approach for cognitive decline.

## 4.3 General limitations and strengths

The limitations and strengths of every single study have already been discussed in detail in the summaries of the studies in Chapter 3. There are, however, some general factors worth discussing when integrating the present research findings in a broader context.

In the present studies, we did not investigate transfer effects of CT or CPT interventions. Transfer effects, which are shown if improvement in one task (the trained task) results in

[4] The manuscript of the data simulation study is in preparation (Mattes & Roheger, 2019, in preparation).

improvement in another, untrained task (the “transfer” task; Jacoby & Ahissar, 2013) have gained intense interest in the CT and CPT research debate (Greenwood & Parasuraman, 2016). Even though there are no clear criteria to define transfer distance, the effects seem to be located on a continuum from near to far transfer (Noack, Lövdén, Schmiedek, & Lindenberger, 2009). Near transfer is defined as the improvement in tasks that are similar to the trained task and that share the same mechanisms and components, whereas far transfer refers to improvement in tasks that measure abilities that are not similar to the trained abilities (Teixeira-Santos et al., 2019). One of the most prominent examples for long-term transfer effects of a CT intervention in healthy older adults is provided by the ACTIVE study, which shows evidence for modest transfer of the effects of CT to cognitive functions at a 5-year follow-up (Willis et al., 2006). In general, the investigation of transfer effects of CT and CPT interventions is of high importance to achieve a holistic training effect. In the present thesis, however, transfer effects were not investigated, as one of the primary goals was to investigate the effectiveness of different kinds of CT (structured vs. unstructured) and to compare the effects of a CT and a CPT, and CPT plus counselling intervention.

Another important aspect, not investigated in the present thesis, is the evaluation of effects of CT and CPT interventions on non-cognitive outcomes such as mood, the ability to function independently, and quality of life. Some studies have already shown that especially CPT interventions might have the potential to improve quality of life in older adults (Elavsky et al., 2005; Langlois et al., 2013), even though the underlying mechanisms are still under debate.

A factor that is often discussed in CT and CPT research is the design of the studies and the related statistical methods for the study analyses (Moreau et al., 2016). Yet, sample sizes of CT and CPT studies are often limited due to study designs and research costs, leading to a lack of power in most CT and CPT studies (Moreau et al., 2016). However, a low power can lead to undetected relevant effects and to significant, yet false positive, results. Therefore, the replication of study findings (as we did in the present thesis in Studies I, II and III in parts) is of high importance (Pashler & Wagenmakers, 2012). A further statistical phenomenon which is regularly discussed in CT and CPT research is “regression to the mean”. “Regression to the mean” is defined as the tendency of a variable that is extreme on its first measurement to be closer to the center of the distribution for a later measurement (Davis, 1976). The “regression to the mean” problem is often made substantially worse by ceiling and floor effects, which are likely to occur in certain neuropsychological tests (Morton & Torgerson, 2005). Smolen et al. (2018) could show in a data simulation study that most of the approaches to measure predictors (especially neuropsychological test performance at study entry as a predictor) of CT and CPT are insufficient and are due to statistical artifacts caused by “regression to the mean”. They propose to use direct modeling of correlations between latent true measures and gain (Smoleń, Jastrzebski, Estrada, & Chuderski, 2018) and highlight the need for more statistical modeling studies to investigate this approach (as the present thesis could also show in Study IV).

The present thesis possesses some important strengths. It is one of the first studies investigating not only short-term predictors of CT, but also long-term predictors of CT improvement. This distinction is of high importance to choose the best fitting nonpharmacological intervention depending on the individual’s goals. Further, it is one of the first studies investigating predictors of CPT success and thereby also focusing on the comparison between predictors of CT and CPT success. Therefore, the present thesis provides an important contribution to the question: “which individual benefits from which kind of training intervention?” and thus to an individual-centered prevention approach for cognitive ageing.

Furthermore, a huge strength of the present thesis is the fact that this is the first study showing that when investigating predictors of training success in general, the tendency of the prognostic factor (the more of x/ the less of x) is conditional on the used dependent outcome measure (post-test scores vs. change scores vs. residual scores). This finding is a substantial contribution for the interpretation of the current literature on prognostic factors of nonpharmacological training success in healthy older adults, because until now it was not clear why the directions of prognostic/predictive factors differed across studies, resulting in competing theories that have been developed to explain contradictory results (Smoleń et al., 2018). Therefore, the present thesis closes a huge research gap by showing that most of these conflicting results are due to different dependent variables and statistical methods used rather than to different underlying mechanisms. Also, the results point out further possible research directions on prognostic/predictive factor research on nonpharmacological intervention success and the effectiveness of nonpharmacological interventions in general, which will be presented and further discussed in the Section 4.4.

A further strength of the present thesis is the clear and transparent reporting of the methods using reporting standards like CONSORT (Boutron, Altman, Moher, Schulz, & Ravaud, 2017) and PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009).

To summarize, the present thesis contributes substantially not only on a content level by showing the effectiveness of CT and CPT interventions and identifying possible predictors of CT and CPT success, but also methodologically by identifying short-comings in predictor research on CT and CPT success so far.

## 4.4 Implications for future research and for every-day life

There are several implications for future research and also for everyday life decisions that can be drawn from the results of the present thesis in the area of nonpharmacological interventions in healthy older adults and predictors for nonpharmacological intervention success.

There is still an ongoing research debate on whether pure CTs, pure PTs, or combined CPTs are the most effective interventions to delay cognitive decline in a healthy ageing process. There are several systematic reviews and meta-analyses that show that all of these interventions have positive effects on cognition (Chiu et al., 2017; Joubert & Chainay, 2018; Northey et al., 2018), as already discussed in Section 1.2. However, to further investigate which of these nonpharmacological interventions is the most effective, further research should focus on conducting a network meta-analysis comparing pure CT, pure PT, and combined CPT with a control group. A network meta-analysis is a technique for comparing multiple treatments simultaneously in a single analysis by combining direct and indirect evidence within a network of RCTs (Rouse, Chaimani, & Li, 2017). Furthermore, subgroup analysis can be conducted to determine which other relevant variables (e.g. sex, duration of training) might have an influence on training effectiveness. These results would be highly relevant not only for healthy older adults who want to maintain their cognitive status, but also for providers of these interventions and policy makers in health care in consideration of choice and promotion of prevention approaches. Our research group has submitted a research grant application to the German Federal Ministry for Research and Education with the aim to conduct this network meta-analysis and to further contribute to this important field of research.

Also, it will be important to conduct further RCTs on CT and CPT interventions in different samples to replicate the results of the present thesis and to further understand possible predictors of CT and CPT success (Pashler & Wagenmakers, 2012). To achieve this it is important to conduct close replications, which should give more precise estimates than the original studies, as well as more general replications, which may increase precision and provide evidence for the generality of the original finding (Cumming, 2014). Therefore, general replications should include more heterogeneous samples with larger sample sizes to provide a preferably wide range of possible predictor variables (e.g. a wide age-range, or education-range within the sample). In samples in most intervention studies in healthy older people, participants are highly motivated and highly educated, and, in general, volunteers in intervention studies may differ in motivation, outcome expectations, sociodemographic variables, and healthy lifestyles (Oswald et al., 2006; Schubert, Strobach, & Karbach, 2014; Unverzagt et al., 2009). Hence, it is important to try to recruit participants with, for example, different socioeconomic status or variable motivational status to be able to assess if these factors are also possible predictors of intervention success. There is a gap between clinical and theoretical goals of intervention studies and typically the design of a given study cannot optimize both (Jacoby & Ahissar, 2013). On the one hand, as already mentioned, it is desirable to have a huge heterogeneity in the sample to detect and define subgroups and possible predictors, on the other hand, clear inclusion and exclusion criteria for a sample are needed to be able to compare study results throughout the literature. A further factor that accounts for the heterogeneity of the investigated sample is the fact that in most published studies and most populations that have been investigated are drawn entirely from Western, educated, industrialized, rich, and democratic (WEIRD) societies (Henrich et al., 2010) implying that there is little variation across human populations and that these "standard subjects" are representative of the whole human population. Yet, empirical patterns suggest that studies should not be based on this rather small and rather unusual population (Henrich et al., 2010; Spector-Mersel, 2006). Also, sex differences should gain more importance in future research studies and, when investigating sex as a predictor for CT success, more attention should be given to the fact that sex is usually categorized as binary (female or male), even though there is variation in the biological attributes that constitute sex and its expression (Heidari et al., 2016).

One of the ultimate goals of prevention research in the long run regarding predictors of nonpharmacological training interventions in healthy older adults with the aim to maintain or even improve cognitive functions is to achieve an individualized prevention approach. A future vision would be that individuals would visit their general health practitioner to express their concerns about a specific "outcome" (e.g., memory, quality of life), and then the practitioner would choose a fitting nonpharmacological intervention approach (e.g. pure CT, PT, or CPT) with specific intervention characteristics (e.g., length, intensity) for the specific individual based on that individual's characteristics (e.g., sociodemographic, neurobiological, psychological, and cognitive variables) that would provide the best results for the outcome the individual is concerned about (for an overview of this procedure and goal see Figure 3). An even more preferable future vision would be that all people who are older than a certain age (e.g. 50 years) get "check-up" appointments even before they have symptoms of subjective cognitive decline and could start with training even before showing symptoms. From the other perspective, health practitioners can identify possible "outcomes of concern" in the individuals and give recommendations for a successful prevention approach. In the long-term, this would also relieve the financial burden on health insurance and the health care system. The overall aim should be to provide an individual-centered, personalized medicine prevention approach. The present thesis made the first steps to achieve this aim in the context of cognitive decline by systematically investigating possible predictors for CT, CPT, and memory training success and in focusing attention on this important topic.

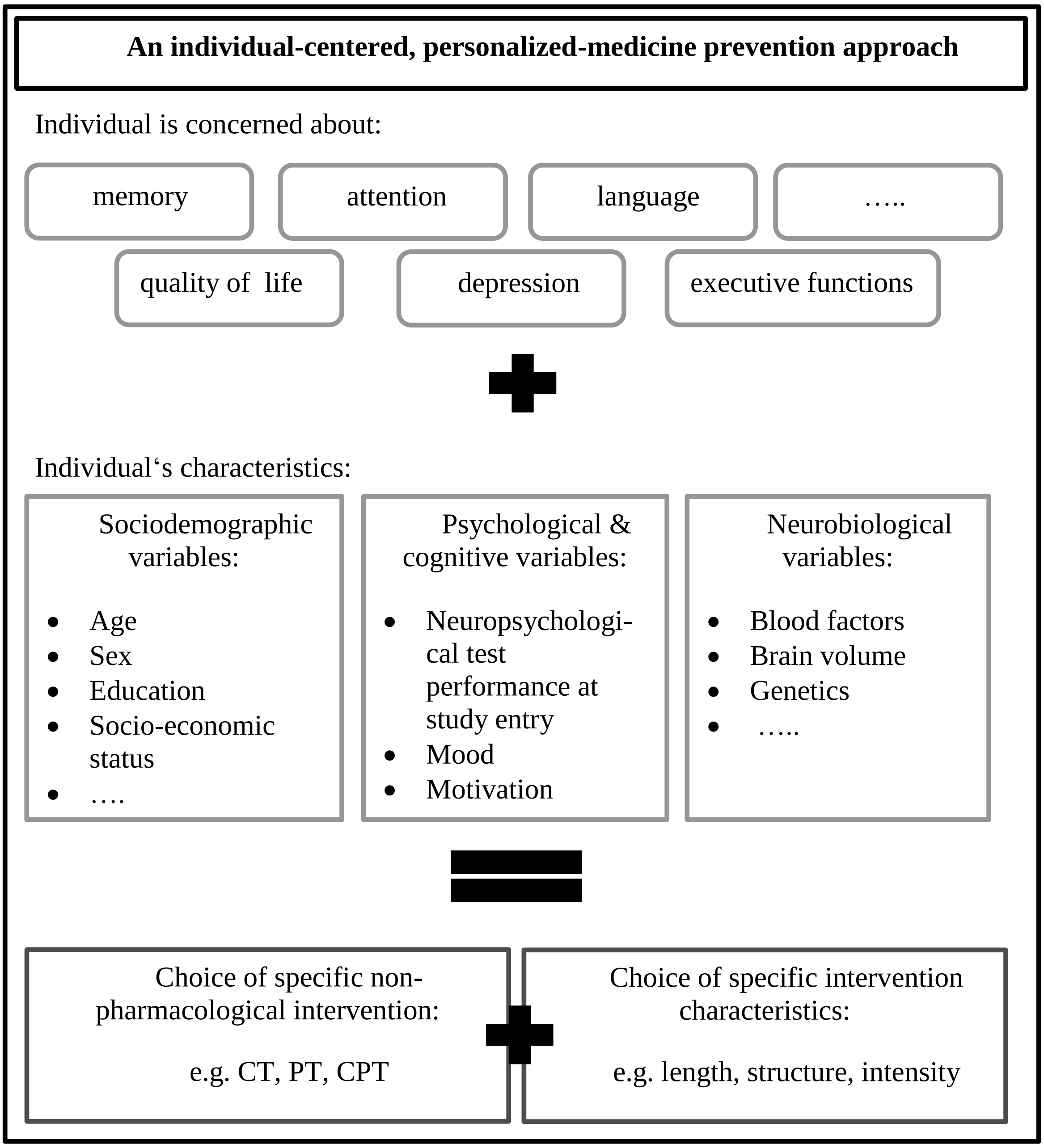


Figure 3: The process of an individual-centered, personalized medicine approach regarding the best choice of nonpharmacological intervention, based on specific individual characteristics, to maintain or even improve specific outcomes.

As already outlined in Section 4.2, the present thesis was the first to show that the tendency of the prognostic factor (the more of x/ the less of x) is conditional on the dependent outcome measure used (post-test scores vs. change scores vs. residual scores) when investigating CT success in healthy older adults. It can be assumed, that this is also the case for other nonpharmacological intervention studies, yet further systematic reviews are needed to confirm this hypothesis. To provide a deeper understanding of prognostic factor research it is important to investigate statistical patterns of the different calculations and dependent variables used for prognostic research, as well as to investigate predictors of CT success in a real-life setting to test the findings in a population of healthy older adults undergoing CT (for more details on these two research ideas see Section 4.2).

Future studies on predictors/prognostic factors of nonpharmacological intervention success should use the prognostic factor recommendation guidelines, which are already implemented in the medical research area (Laupacis, Sekar, & Stiell, 1997; Moons et al., 2014), but seem to be fairly new in the context of prognostic/predictive research in the fields of neuropsychology or psychology in general, as the present thesis could show in the context of memory training success in healthy older adults (Study IV).

To summarize, an implication of the findings of the present thesis for every-day life is that results show that nonpharmacological interventions are a promising approach to maintain and improve cognitive functions in the ageing process. Furthermore, the fact that more “vulnerable” groups seem to profit most from these interventions, also implies that it is never too late to start working on one’s cognitive functions to maintain a high quality of life throughout the ageing process.

## 4.5 Conclusion

The present thesis showed that both CT and CPT interventions can help to maintain and improve cognitive functions in healthy older adults. Therefore, healthy older adults should use CT and CPT to prevent cognitive ageing. Furthermore, as one of the first studies to do so, the present thesis identified short-and long-term predictors for CT success, as well as long-term predictors for CPT success and compared these. Results indicate that especially more “vulnerable” groups (participants with lower education and a lower neuropsychological test performance at study entry) seem to profit more from CT and CPT interventions both short and long term. Furthermore, sex differences were observed. Additionally, the present thesis showed that the literature on predictors of memory training success, a special form of CT, indicates apparently inconsistent results. However, we identified that these inconsistent results are caused by different statistical methods and the use of different dependent variables for the prediction calculation and could thereby systematize the evidence on CT success predictors.

In summary, the present thesis contributes substantially to the research area of the effectiveness of CT and CPT interventions, as well as predictors for intervention success, thus making an important contribution to an individualized prevention approach to maintaining cognitive abilities in healthy older ageing.

## *5.* References


Adlard, P. A., Perreau, V. M., Pop, V., & Cotman, C. W. [Carl] (2005). Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. *The Journal of Neuroscience : the Official Journal of the Society for Neuroscience*, *25*(17), 4217–4221. https://doi.org/10.1523/JNEUROSCI.0496-05.2005

Alfred Rütten & Klaus Pfeifer (Ed.). (2016). Nationale Empfehlungen für Bewegung und Bewegungsförderung [Special issue]: Bundesministerium für Gesundheit. Retrieved from https://www.sport.fau.de/files/2016/05/Nationale-Empfehlungen-f%C3%BCr-Bewegung-und-Bewegungsf%C3%B6rderung-2016.pdf

Angelucci, F., Peppe, A., Carlesimo, G. A., Serafini, F., Zabberoni, S., Barban, F., . . . Costa, A. (2015). A pilot study on the effect of cognitive training on BDNF serum levels in individuals with Parkinson's disease. *Frontiers in Human Neuroscience*, *9*, 130. https://doi.org/10.3389/fnhum.2015.00130

Bäckman, L., & Nyberg, L. (2013). Dopamine and training-related working-memory improvement. *Neuroscience and Biobehavioral Reviews*, *37*(9 Pt B), 2209–2219. https://doi.org/10.1016/j.neubiorev.2013.01.014

Bahar-Fuchs, A., Clare, L. [Linda], & Woods, B. (2013). Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. *The Cochrane Database of Systematic Reviews*. (6), CD003260. https://doi.org/10.1002/14651858.CD003260.pub2

Bahar-Fuchs, A., Martyr, A., Goh, A. M., Sabates, J., & Clare, L. [Linda] (2019). Cognitive training for people with mild to moderate dementia. *The Cochrane Database of Systematic Reviews, 3,* CD013069. https://doi.org/10.1002/14651858.CD013069.pub2

Ball, K., Berch, D. B., Helmers, K. F., Jobe, J. B., Leveck, M. D., Marsiske, M., . . . Willis, S. L. (2002). Effects of cognitive training interventions with older adults: A randomized controlled trial. *JAMA*, *288*(18), 2271–2281.

Ball, K., Edwards, J. D., & Ross, L. A. (2007). The impact of speed of processing training on cognitive and everyday functions. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *62 Spec No 1*, 19–31.

Baller, G., Kalbe, E. [Elke], Kaesberg, S. [Stephanie], & Kessler, J. [Josef]. (2009). *NEUROvitalis*: ProLog.

Baltes (1993). The ageing mind: Potential and limits. *The Gerontologist*, *33*(5), 580–594.

Baltes, Sowarka, D. [Doris], & Kliegl, R. (1989). Cognitive training research on fluid intelligence in old age: What can older adults achieve by themselves? *Psychology and Ageing*, *4*(2), 217–221. https://doi.org/10.1037/0882-7974.4.2.217

Baltes, M. M., Kühl, K. P., Gutzmann, H., & Sowarka, D. (1995). Potential of cognitive plasticity as a diagnostic instrument: A cross-validation and extension. *Psychology and Ageing*, *10*(2), 167–172.

Bamidis, P. D., Vivas, A. B., Styliadis, C., Frantzidis, C., Klados, M., Schlee, W., . . . Papageorgiou, S. G. (2014). A review of physical and cognitive interventions in ageing. *Neuroscience and Biobehavioral Reviews*, *44*, 206–220. https://doi.org/10.1016/j.neubiorev.2014.03.019

Barha, C. K., Davis, J. C., Falck, R. S., Nagamatsu, L. S., & Liu-Ambrose, T. (2017). Sex differences in exercise efficacy to improve cognition: A systematic review and meta-analysis of randomized controlled trials in older humans. *Frontiers in Neuroendocrinology*, *46*, 71–85. https://doi.org/10.1016/j.yfrne.2017.04.002

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of general psychiatry*, *4*(6), 561–571.

Beinhoff, U., Tumani, H., Brettschneider, J., Bittner, D., & Riepe, M. W. (2008). Gender-specificities in Alzheimer's disease and mild cognitive impairment. *Journal of Neurology*, *255*(1), 117–122. https://doi.org/10.1007/s00415-008-0726-9

Bekinschtein, P., Cammarota, M., Katche, C., Slipczuk, L., Rossato, J. I., Goldin, A., . . . Medina, J. H. (2008). Bdnf is essential to promote persistence of long-term memory storage. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(7), 2711–2716. https://doi.org/10.1073/pnas.0711863105

Belleville, S., & Bherer, L. (2012). Biomarkers of Cognitive Training Effects in Ageing. *Current Translational Geriatrics and Experimental Gerontology Reports*, *1*(2), 104–110. https://doi.org/10.1007/s13670-012-0014-5

Bender, A. R., Völkle, M. C., & Raz, N. (2016). Differential ageing of cerebral white matter in middle-aged and older adults: A seven-year follow-up. *NeuroImage*, *125*, 74–83. https://doi.org/10.1016/j.neuroimage.2015.10.030

Bherer, L. (2015). Cognitive plasticity in older adults: Effects of cognitive training and physical exercise. *Annals of the New York Academy of Sciences*, *1337*, 1–6. https://doi.org/10.1111/nyas.12682

Bherer, L., Kramer, A. F., Peterson, M. S., Colcombe, S., Erickson, K., & Becic, E. (2005). Training effects on dual-task performance: Are there age-related differences in plasticity of attentional control? *Psychology and Ageing*, *20*(4), 695–709. https://doi.org/10.1037/0882-7974.20.4.695

Biddle, S., & Mutrie, N. (1991). Psychology of physical activity and exercise. *Psychology of physical activity and exercise*.

Bissig, D., & Lustig, C. (2007). Who benefits from memory training? *Psychological Science*, *18*(8), 720–726. https://doi.org/10.1111/j.1467-9280.2007.01966.x

Blazer, D. G., Yaffe, K., & Liverman, C. T. (Eds.). (2015). *Cognitive Ageing: Progress in Understanding and Opportunities for Action*. Washington (DC). https://doi.org/10.17226/21693

Boot, W. R., Simons, D. J., Stothart, C., & Stutts, C. (2013). The Pervasive Problem With Placebos in Psychology: Why Active Control Groups Are Not Sufficient to Rule Out Placebo Effects. *Perspectives on Psychological Science : a Journal of the Association for Psychological Science*, *8*(4), 445–454. https://doi.org/10.1177/1745691613491271

Boron, J. B., Turiano, N. A., Willis, S. L., & Schaie, K. W. [K. Warner] (2007). Effects of cognitive training on change in accuracy in inductive reasoning ability. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *62*(3), P179-86.

Boutron, I., Altman, D. G., Moher, D., Schulz, K. F., & Ravaud, P. (2017). Consort Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Annals of Internal Medicine*, *167*(1), 40–47. https://doi.org/10.7326/M17-0046

Boyke, J., Driemeyer, J., Gaser, C., Büchel, C., & May, A. (2008). Training-induced brain structure changes in the elderly. *The Journal of Neuroscience : the Official Journal of the Society for Neuroscience*, *28*(28), 7031–7035. https://doi.org/10.1523/JNEUROSCI.0742-08.2008

Brayne, C. (2007). The elephant in the room - healthy brains in later life, epidemiology and public health. *Nature Reviews. Neuroscience, 8*(3), 233–239. https://doi.org/10.1038/nrn2091

Brehmer, Y., Kalpouzos, G., Wenger, E., & Lövdén, M. (2014). Plasticity of brain and cognition in older adults. *Psychological Research*, *78*(6), 790–802. https://doi.org/10.1007/s00426-014-0587-z

Brehmer, Y., Westerberg, H., & Bäckman, L. [Lars] (2012). Working-memory training in younger and older adults: Training gains, transfer, and maintenance. *Frontiers in Human Neuroscience*, *6*, 63. https://doi.org/10.3389/fnhum.2012.00063

Brooks, J. O., Friedman, L. [Leah], Pearman, A. M. [Ann], Gray, C. [Christine], & Yesavage, J. A. [Jerome] (1999a). Mnemonic Training in Older Adults: Effects of Age, Length of Training, and Type of Cognitive Pretraining. *International psychogeriatrics, 11*(1), 75–84. https://doi.org/10.1017/S1041610299005608

Brooks, J. O., Friedman, L., Pearman, A. M., Gray, C., & Yesavage, J. A. (1999b). Mnemonic training in older adults: Effects of age, length of training, and type of cognitive pretraining. *International Psychogeriatrics*, *11*(1), 75–84.

Buckner, R. L. (2004). Memory and executive function in ageing and AD: Multiple factors that cause decline and reserve factors that compensate. *Neuron*, *44*(1), 195–208. https://doi.org/10.1016/j.neuron.2004.09.006

Buonomano, D. V., & Merzenich, M. M. (1998). Cortical plasticity: From synapses to maps. *Annual Review of Neuroscience*, *21*, 149–186. https://doi.org/10.1146/annurev.neuro.21.1.149

Buschert, V., Bokde, A. L. W., & Hampel, H. (2010). Cognitive intervention in Alzheimer disease. *Nature Reviews. Neurology*, *6*(9), 508–517. https://doi.org/10.1038/nrneurol.2010.113

Calero, M. D., & Navarro, E. (2007). Cognitive plasticity as a modulating variable on the effects of memory training in elderly persons. *Archives of Clinical Neuropsychology : the Official Journal of the National Academy of Neuropsychologists*, *22*(1), 63–72. https://doi.org/10.1016/j.acn.2006.06.020

Carroll, S., & Dudfield, M. (2004). What is the relationship between exercise and metabolic abnormalities? A review of the metabolic syndrome. *Sports Medicine (Auckland, N.Z.)*, *34*(6), 371–418. https://doi.org/10.2165/00007256-200434060-00004

Cassilhas, R. C., Viana, V. A. R., Grassmann, V., Santos, R. T. [Ronaldo], Santos, R. F. [Ruth], Tufik, S., & Mello, M. T. (2007). The impact of resistance exercise on the cognitive function of the elderly. *Medicine and Science in Sports and Exercise*, *39*(8), 1401–1407. https://doi.org/10.1249/mss.0b013e318060111f

Cespón, J., Miniussi, C., & Pellicciari, M. C. (2018). Interventional programmes to improve cognition during healthy and pathological ageing: Cortical modulations and evidence for brain plasticity. *Ageing Research Reviews, 43,* 81–98. https://doi.org/10.1016/j.arr.2018.03.001

Chapman, S. B., Aslan, S., Spence, J. S., Hart, J. J., Bartz, E. K., Didehbani, N., . . . Lu, H. (2015). Neural mechanisms of brain plasticity with complex cognitive training in healthy seniors. *Cerebral Cortex (New York, N.Y. : 1991)*, *25*(2), 396–405. https://doi.org/10.1093/cercor/bht234

Chen, R., Cohen, L. G., & Hallett, M. (2002). Nervous system reorganization following injury. *Neuroscience*, *111*(4), 761–773.

Chiu, H.‑L., Chu, H., Tsai, J.‑C., Liu, D., Chen, Y.‑R. [Ying-Ren], Yang, H.‑L., & Chou, K.‑R. (2017). The effect of cognitive-based training for the healthy older people: A meta-analysis of randomized controlled trials. *PLoS ONE*, *12*(5). https://doi.org/10.1371/journal.pone.0176742

Clare, L., Woods, R. T., Moniz Cook, E. D., Orrell, M., & Spector, A. (2003). Cognitive rehabilitation and cognitive training for early-stage Alzheimer's disease and vascular dementia. *The Cochrane Database of Systematic Reviews*. (4), CD003260. https://doi.org/10.1002/14651858.CD003260

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychological Science*, *14*(2), 125–130. https://doi.org/10.1111/1467-9280.t01-1-01430

Corbett, A., Owen, A., Hampshire, A., Grahn, J., Stenton, R., Dajani, S., . . . Ballard, C. (2015). The Effect of an Online Cognitive Training Package in Healthy Older Adults: An Online Randomized Controlled Trial. *Journal of the American Medical Directors Association*, *16*(11), 990–997. https://doi.org/10.1016/j.jamda.2015.06.014

Cotman, C. W. [Carl], & Berchtold, N. C. (2002). Exercise: A behavioral intervention to enhance brain health and plasticity. *Trends in Neurosciences*, *25*(6), 295–301.

Cotman, C. W. [Carl], Berchtold, N. C., & Christie, L.‑A. (2007). Exercise builds brain health: Key roles of growth factor cascades and inflammation. *Trends in Neurosciences*, *30*(9), 464–472. https://doi.org/10.1016/j.tins.2007.06.011

Cowell, P. E., Allen, L. S., Zalatimo, N. S., & Denenberg, V. H. (1992). A developmental study of sex and age interactions in the human corpus callosum. *Brain Research. Developmental Brain Research*, *66*(2), 187–192.

Cumming, G. (2014). The new statistics: Why and how. *Psychological Science*, *25*(1), 7–29. https://doi.org/10.1177/0956797613504966

Curlik, D. M., & Shors, T. J. (2013). Training your brain: Do mental and physical (MAP) training enhance cognition through the process of neurogenesis in the hippocampus? *Neuropharmacology*, *64*, 506–514. https://doi.org/10.1016/j.neuropharm.2012.07.027

Curran-Everett, D. (2013). Explorations in statistics: The analysis of ratios and normalized data. *Advances in Physiology Education*, *37*(3), 213–219. https://doi.org/10.1152/advan.00053.2013

Davis, C. E. (1976). The effect of regression to the mean in epidemiologic and clinical studies. *American Journal of Epidemiology*, *104*(5), 493–498. https://doi.org/10.1093/oxfordjournals.aje.a112321

Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., . . . Starr, J. M. (2009). Age-associated cognitive decline. *British Medical Bulletin*, *92*, 135–152. https://doi.org/10.1093/bmb/ldp033

Debray, T. P. A., Damen, J. A. A. G., Snell, K. I. E., Ensor, J., Hooft, L., Reitsma, J. B., . . . Moons, K. G. M. (2017). A guide to systematic review and meta-analysis of prediction model performance. *BMJ (Clinical Research Ed.)*, *356*, i6460. https://doi.org/10.1136/bmj.i6460

Desjardins-Crépeau, L., Berryman, N., Fraser, S. A., Vu, T. T. M., Kergoat, M.‑J., Li, K. Z. H., . . . Bherer, L. (2016). Effects of combined physical and cognitive training on fitness and neuropsychological outcomes in healthy older adults. *Clinical Interventions in Ageing*, *11*, 1287–1299. https://doi.org/10.2147/CIA.S115711

Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., & May, A. (2004). Neuroplasticity: Changes in grey matter induced by training. *Nature*, *427*(6972), 311–312. https://doi.org/10.1038/427311a

Duckworth, A. L., Quinn, P. D., Lynam, D. R., Loeber, R., & Stouthamer-Loeber, M. (2011). Role of test motivation in intelligence testing. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(19), 7716–7720. https://doi.org/10.1073/pnas.1018601108

Elavsky, S., McAuley, E., Motl, R. W., Konopack, J. F., Marquez, D. X., Hu, L., . . . Diener, E. (2005). Physical activity enhances long-term quality of life in older adults: Efficacy, esteem, and affective influences. *Annals of Behavioral Medicine : a Publication of the Society of Behavioral Medicine*, *30*(2), 138–145. https://doi.org/10.1207/s15324796abm3002_6

Erickson, K. I. [Kirk I.], Gildengers, A. G., & Butters, M. A. (2013). Physical activity and brain plasticity in late adulthood. *Dialogues in Clinical Neuroscience*, *15*(1), 99–108.

Fabre, C., Chamari, K., Mucci, P., Massé-Biron, J., & Préfaut, C. (2002). Improvement of cognitive function by mental and/or individualized aerobic training in healthy elderly subjects. *International Journal of Sports Medicine*, *23*(6), 415–421. https://doi.org/10.1055/s-2002-33735

Fairchild, J. K., Friedman, L., Rosen, A. C., & Yesavage, J. A. (2013). Which older adults maintain benefit from cognitive training? Use of signal detection methods to identify long-term treatment gains. *International Psychogeriatrics*, *25*(4), 607–616. https://doi.org/10.1017/S1041610212002049

Fandakova, Y., Shing, Y. L., & Lindenberger, U. (2012). Heterogeneity in memory training improvement among older adults: A latent class analysis. *Memory (Hove, England)*, *20*(6), 554–567. https://doi.org/10.1080/09658211.2012.687051

Feng, W., Yokoyama, J. S., Yu, S., Chen, Y. [You], Cheng, Y., Bonham, L. W., . . . Li, C. (2015). Apoe Genotype Affects Cognitive Training Response in Healthy Shanghai Community-Dwelling Elderly Individuals. *Journal of Alzheimer's Disease : JAD*, *47*(4), 1035–1046. https://doi.org/10.3233/JAD-150039

Fernandez, A. M., & Torres-Alemán, I. (2012). The many faces of insulin-like peptide signalling in the brain. *Nature Reviews. Neuroscience*, *13*(4), 225–239. https://doi.org/10.1038/nrn3209

Fillit, H., Nash, D. T., Rundek, T., & Zuckerman, A. (2008). Cardiovascular risk factors and dementia. *The American Journal of Geriatric Pharmacotherapy*, *6*(2), 100–118. https://doi.org/10.1016/j.amjopharm.2008.06.004

Finkel, S. I., & Yesavage, J. A. (1989). Learning mnemonics: A preliminary evaluation of a computer-aided instruction package for the elderly. *Experimental Ageing Research*, *15*(3-4), 199–201. https://doi.org/10.1080/03610738908259776

Fjell, A. M., McEvoy, L., Holland, D., Dale, A. M., & Walhovd, K. B. (2014). What is normal in normal ageing? Effects of ageing, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. *Progress in Neurobiology*, *117*, 20–40. https://doi.org/10.1016/j.pneurobio.2014.02.004

Foster, C., Hillsdon, M., Thorogood, M., Kaur, A., & Wedatilake, T. (2005). Interventions for promoting physical activity. *The Cochrane Database of Systematic Reviews*. (1), CD003180. https://doi.org/10.1002/14651858.CD003180.pub2

Fruyt, F. de, McCrae, R. R., Szirmák, Z., & Nagy, J. (2004). The Five-factor Personality Inventory as a measure of the Five-factor Model: Belgian, American, and Hungarian comparisons with the NEO-PI-R. *Assessment*, *11*(3), 207–215. https://doi.org/10.1177/1073191104265800

Gallagher, M., & Rapp, P. R. (1997). The use of animal models to study the effects of ageing on cognition. *Annual Review of Psychology*, *48*, 339–370. https://doi.org/10.1146/annurev.psych.48.1.339

Riddle, D. R. (Ed.). (2007). *Brain Ageing: Models, Methods, and Mechanisms: Changes in Cognitive Function in Human Ageing*. Boca Raton (FL).

Grady, C. L. (2008). Cognitive neuroscience of ageing. *Annals of the New York Academy of Sciences*, *1124*, 127–144. https://doi.org/10.1196/annals.1440.009

Greenwood, P. M., & Parasuraman, R. (2016). The mechanisms of far transfer from cognitive training: Review and hypothesis. *Neuropsychology*, *30*(6), 742–755. https://doi.org/10.1037/neu0000235

Gur, R. C. [R. C.], Alsop, D., Glahn, D., Petty, R., Swanson, C. L., Maldjian, J. A., . . . Gur, R. E. [R. E.] (2000). An fMRI study of sex differences in regional activation to a verbal and a spatial task. *Brain and Language*, *74*(2), 157–170. https://doi.org/10.1006/brln.2000.2325

Habib, R., Nyberg, L., & Nilsson, L.‐G. (2007). Cognitive and non-cognitive factors contributing to the longitudinal identification of successful older adults in the betula study. *Neuropsychology, Development, and Cognition. Section B, Ageing, Neuropsychology and Cognition*, *14*(3), 257–273. https://doi.org/10.1080/13825580600582412

Hamer, M., & Chida, Y. (2009). Physical activity and risk of neurodegenerative disease: A systematic review of prospective evidence. *Psychological Medicine*, *39*(1), 3–11. https://doi.org/10.1017/S0033291708003681

Hartshorne, J. K., & Germine, L. T. (2015). When does cognitive functioning peak? The asynchronous rise and fall of different cognitive abilities across the life span. *Psychological Science*, *26*(4), 433–443. https://doi.org/10.1177/0956797614567339

Hayden, J. A. [Jill A.], van der Windt, D. A., Cartwright, J. L., Côté, P., & Bombardier, C. (2013). Assessing bias in studies of prognostic factors. *Annals of Internal Medicine, 158*(4), 280–286. https://doi.org/10.7326/0003-4819-158-4-201302190-00009

Hedden, T., & Gabrieli, J. D. E. (2004). Insights into the ageing mind: A view from cognitive neuroscience. *Nature Reviews. Neuroscience, 5*(2), 87–96. https://doi.org/10.1038/nrn1323

Heidari, S., Babor, T. F., Castro, P. de, Tort, S., & Curno, M. (2016). Sex and Gender Equity in Research: Rationale for the SAGER guidelines and recommended use. *Research Integrity and Peer Review*, *1*, 2. https://doi.org/10.1186/s41073-016-0007-6

Henrich, J., Heine, S. J., & Norenzayan, A. (2010). The weirdest people in the world? *The Behavioral and Brain Sciences*, *33*(2-3), 61-83; discussion 83-135. https://doi.org/10.1017/S0140525X0999152X

Hötting, K., & Röder, B. (2013). Beneficial effects of physical exercise on neuroplasticity and cognition. *Neuroscience and Biobehavioral Reviews, 37*(9 Pt B), 2243–2257. https://doi.org/10.1016/j.neubiorev.2013.04.005

Jack, Albert, M. S. [Marilyn], Knopman, D. S., McKhann, G. M., Sperling, R. A., Carrillo, M. C., . . . Phelps, C. H. (2011). Introduction to the recommendations from the National Institute on Ageing-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia : the Journal of the Alzheimer's Association*, *7*(3), 257–262. https://doi.org/10.1016/j.jalz.2011.03.004

Jacoby, N., & Ahissar, M. (2013). What does it take to show that a cognitive training procedure is useful? A critical evaluation. *Progress in Brain Research, 207*, 121–140. https://doi.org/10.1016/B978-0-444-63327-9.00004-7

Jaeggi, S. M., Buschkuehl, M., Jonides, J., & Perrig, W. J. (2008). Improving fluid intelligence with training on working memory. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(19), 6829–6833. https://doi.org/10.1073/pnas.0801268105

Jiang, J., Fiocco, A. J., Cao, X., Jiang, L., Feng, W., Shen, Y., . . . Li, C. (2018). The Moderating Role of COMT and BDNF Polymorphisms on Transfer Effects Following Multi- and Single-Domain Cognitive Training Among Community-Dwelling Shanghainese Older Adults. *Frontiers in Ageing Neuroscience*, *10.* https://doi.org/10.3389/fnagi.2018.00198

Jockwitz, C., Mérillat, S., Liem, F., Oschwald, J., Amunts, K., Caspers, S., & Jäncke, L. (2019). Generalizing age effects on brain structure and cognition: A two-study comparison approach. *Human Brain Mapping.* Advance online publication. https://doi.org/10.1002/hbm.24524

Joubert, C., & Chainay, H. (2018). Ageing brain: The effect of combined cognitive and physical training on cognition as compared to cognitive and physical training alone - a systematic review. *Clinical Interventions in Ageing*, *13*, 1267–1301. https://doi.org/10.2147/CIA.S165399

Kalbe, E. [Elke], Roheger, M., Paluszak, K., Meyer, J., Becker, J., Fink, G. R. [Gereon], . . . Kessler, J. [Josef] (2018). Effects of a Cognitive Training With and Without Additional Physical Activity in Healthy Older Adults: A Follow-Up 1 Year After a Randomized Controlled Trial. *Frontiers in Ageing Neuroscience*, *10*, 407. https://doi.org/10.3389/fnagi.2018.00407

Kattenstroth, J.‐C., Kalisch, T., Holt, S., Tegenthoff, M., & Dinse, H. R. (2013). Six months of dance intervention enhances postural, sensorimotor, and cognitive performance in elderly without affecting cardio-respiratory functions. *Frontiers in Ageing Neuroscience*, *5*. https://doi.org/10.3389/fnagi.2013.00005

Kelly, M. E., Loughrey, D., Lawlor, B. A., Robertson, I. H., Walsh, C., & Brennan, S. (2014). The impact of cognitive training and mental stimulation on cognitive and everyday functioning of healthy older adults: A systematic review and meta-analysis. *Ageing Research Reviews*, *15*, 28–43. https://doi.org/10.1016/j.arr.2014.02.004

Kessler, J. [Josef], Calabrese, P., Kalbe, E., & Berger, F. (2000). DemTect: Ein neues Screening-Verfahren zur Unterstützung der Demenzdiagnostik. *Psycho*, *26*, 343–347.

Knaepen, K., Goekint, M., Heyman, E. M., & Meeusen, R. (2010). Neuroplasticity - exercise-induced response of peripheral brain-derived neurotrophic factor: A systematic review of experimental studies in human subjects. *Sports Medicine (Auckland, N.Z.)*, *40*(9), 765–801. https://doi.org/10.2165/11534530-000000000-00000

Kraft, E. (2012). Cognitive function, physical activity, and ageing: Possible biological links and implications for multimodal interventions. *Neuropsychology, Development, and Cognition. Section B, Ageing, Neuropsychology and Cognition*, *19*(1-2), 248–263. https://doi.org/10.1080/13825585.2011.645010

Kramer, A. F., & Colcombe, S. (2018). Fitness Effects on the Cognitive Function of Older Adults: A Meta-Analytic Study-Revisited. *Perspectives on Psychological Science : a Journal of the Association for Psychological Science*, *13*(2), 213–217. https://doi.org/10.1177/1745691617707316

Krieger, N., Williams, D. R., & Moss, N. E. (1997). Measuring social class in US public health research: Concepts, methodologies, and guidelines. *Annual Review of Public Health*, *18*, 341–378. https://doi.org/10.1146/annurev.publhealth.18.1.341

Lampit, A., Hallock, H., & Valenzuela, M. (2014). Computerized cognitive training in cognitively healthy older adults: A systematic review and meta-analysis of effect modifiers. *PLoS Medicine*, *11*(11), e1001756. https://doi.org/10.1371/journal.pmed.1001756

Langbaum, J. B. S., Rebok, G. W., Bandeen-Roche, K., & Carlson, M. C. (2009). Predicting memory training response patterns: Results from ACTIVE. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *64*(1), 14–23. https://doi.org/10.1093/geronb/gbn026

Lange, A.‑M. G. de, Bråthen, A. C. S., Grydeland, H., Sexton, C., Johansen-Berg, H., Andersson, J. L. R., . . . Walhovd, K. B. (2016). White matter integrity as a marker for cognitive plasticity in ageing. *Neurobiology of Ageing*, *47*, 74–82. https://doi.org/10.1016/j.neurobiolageing.2016.07.007

Langlois, F., Vu, T. T. M., Chassé, K., Dupuis, G., Kergoat, M.‑J., & Bherer, L. (2013). Benefits of Physical Exercise Training on Cognition and Quality of Life in Frail Older Adults. *The Journals of Gerontology: Series B*, *68*(3), 400–404. https://doi.org/10.1093/geronb/gbs069

Lauenroth, A., Ioannidis, A. E., & Teichmann, B. (2016). Influence of combined physical and cognitive training on cognition: A systematic review. *BMC Geriatrics*, *16*, 141. https://doi.org/10.1186/s12877-016-0315-1

Laupacis, A., Sekar, N., & Stiell, I. G. (1997). Clinical prediction rules. A review and suggested modifications of methodological standards. *JAMA*, *277*(6), 488–494.

Law, L. L. F., Barnett, F., Yau, M. K., & Gray, M. A. (2014). Effects of combined cognitive and exercise interventions on cognition in older adults with and without cognitive impairment: A systematic review. *Ageing Research Reviews*, *15*, 61–75. https://doi.org/10.1016/j.arr.2014.02.008

Lee, H. [HyunKyu], Boot, W. R., Basak, C., Voss, M. W., Prakash, R. S., Neider, M., . . . Kramer, A. F. (2012). Performance gains from directed training do not transfer to untrained tasks. *Acta Psychologica*, *139*(1), 146–158. https://doi.org/10.1016/j.actpsy.2011.11.003

Lehert, P., Villaseca, P., Hogervorst, E., Maki, P. M., & Henderson, V. W. (2015). Individually modifiable risk factors to ameliorate cognitive ageing: A systematic review and meta-analysis. *Climacteric : the Journal of the International Menopause Society*, *18*(5), 678–689. https://doi.org/10.3109/13697137.2015.1078106

Li, Todorovic, R., Devanesan, P., Higginbotham, S., Köfeler, H., Ramanathan, R., . . . Cavalieri, E. L. (2004). Metabolism and DNA binding studies of 4-hydroxyestradiol and estradiol-3,4-quinone in vitro and in female ACI rat mammary gland in vivo. *Carcinogenesis*, *25*(2), 289–297. https://doi.org/10.1093/carcin/bgg191

Li, S.‑C., Schmiedek, F., Huxhold, O., Röcke, C., Smith, J., & Lindenberger, U. (2008). Working memory plasticity in old age: Practice gain, transfer, and maintenance. *Psychology and Ageing*, *23*(4), 731–742. https://doi.org/10.1037/a0014343

Linde, K., & Alfermann, D. (2014). Single versus combined cognitive and physical activity effects on fluid cognitive abilities of healthy older adults: A 4-month randomized controlled trial with follow-up. *Journal of Ageing and Physical Activity*, *22*(3), 302–313. https://doi.org/10.1123/japa.2012-0149

Linn, M. C., & Petersen, A. C. (1985). Emergence and characterization of sex differences in spatial ability: A meta-analysis. *Child Development*, *56*(6), 1479–1498.

Lista, I., & Sorrentino, G. (2010). Biological mechanisms of physical activity in preventing cognitive decline. *Cellular and Molecular Neurobiology*, *30*(4), 493–503. https://doi.org/10.1007/s10571-009-9488-x

Liu, C.‑C. [Chia-Chen], Liu, C.‑C. [Chia-Chan], Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: Risk, mechanisms and therapy. *Nature Reviews. Neurology*, *9*(2), 106–118. https://doi.org/10.1038/nrneurol.2012.263

Liu, W., Ye, P., O'Kusky, J. R. [John R.], & D'Ercole, A. J. (2009). Type 1 insulin-like growth factor receptor signaling is essential for the development of the hippocampal formation and dentate gyrus. *Journal of Neuroscience Research*, *87*(13), 2821–2832. https://doi.org/10.1002/jnr.22129

Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., . . . Mukadam, N. (2017). Dementia prevention, intervention, and care. *The Lancet, 390*(10113), 2673–2734. https://doi.org/10.1016/S0140-6736(17)31363-6

López-Higes, R., Martín-Aragoneses, M. T., Rubio-Valdehita, S., Delgado-Losada, M. L., Montejo, P., Montenegro, M., . . . López-Sanz, D. (2018). Efficacy of Cognitive Training in Older Adults with and without Subjective Cognitive Decline Is Associated with Inhibition Efficiency and Working Memory Span, Not with Cognitive Reserve. *Frontiers in Ageing Neuroscience, 10.* https://doi.org/10.3389/fnagi.2018.00023

Lord, F. M. (1967). A paradox in the interpretation of group comparisons. *Psychological Bulletin*, *68*(5), 304–305.

Lövdén, M., Brehmer, Y., Li, S.‑C., & Lindenberger, U. (2012). Training-induced compensation versus magnification of individual differences in memory performance. *Frontiers in Human Neuroscience, 6.* https://doi.org/10.3389/fnhum.2012.00141

Lussier, M., Brouillard, P., & Bherer, L. (2017). Limited Benefits of Heterogeneous Dual-Task Training on Transfer Effects in Older Adults. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences, 72*(5), 801–812. https://doi.org/10.1093/geronb/gbv105

Mandolesi, L., Gelfo, F., Serra, L., Montuori, S., Polverino, A., Curcio, G., & Sorrentino, G. [Giuseppe] (2017). Environmental Factors Promoting Neural Plasticity: Insights from Animal and Human Studies. *Neural Plasticity, 2017*, 7219461. https://doi.org/10.1155/2017/7219461

Marcus, B. H., & Forsyth, L. H. (2009). Motivating people to be physically active. *Motivating people to be physically active*. (Ed. 2).

Marshall, V. W. (1995). Social Models of Ageing. *Canadian Journal on Ageing / La Revue canadienne du vieillissement*, *14*(01), 12–34. https://doi.org/10.1017/S071498080001045X

Martin, M., Clare, L. [Linda], Altgassen, A. M., Cameron, M. H., & Zehnder, F. (2011). Cognition-based interventions for healthy older people and people with mild cognitive impairment. *The Cochrane Database of Systematic Reviews*. (1), CD006220. https://doi.org/10.1002/14651858.CD006220.pub2

Megyesiová, S., & Hajduová, Z. (2012). Demographic challenges across the European Union Member States. *Workplace Health & Safety*, *60*(7), 321–326. https://doi.org/10.1177/216507991206000706

Millán-Calenti, J. C., Lorenzo, T., Núñez-Naveira, L., Buján, A., Rodríguez-Villamil, J. L., & Maseda, A. (2015). Efficacy of a computerized cognitive training application on cognition and depressive symptomatology in a group of healthy older adults: A randomized controlled trial. *Archives of Gerontology and Geriatrics*, *61*(3), 337–343. https://doi.org/10.1016/j.archger.2015.08.015

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Moons, K. G. M., Groot, J. A. H. de, Bouwmeester, W., Vergouwe, Y., Mallett, S., Altman, D. G., . . . Collins, G. S. (2014). Critical appraisal and data extraction for systematic reviews of prediction modelling studies: The CHARMS checklist. *PLoS Medicine*, *11*(10), e1001744. https://doi.org/10.1371/journal.pmed.1001744

Moreau, D., Kirk, I. J., & Waldie, K. E. (2016). Seven Pervasive Statistical Flaws in Cognitive Training Interventions. *Frontiers in Human Neuroscience, 10*, 153. https://doi.org/10.3389/fnhum.2016.00153

Mortimer, J. A., Ding, D., Borenstein, A. R., DeCarli, C. [Charles], Guo, Q., Wu, Y., . . . Chu, S. (2012). Changes in brain volume and cognition in a randomized trial of exercise and social interaction in a community-based sample of non-demented Chinese elders. *Journal of Alzheimer's Disease : JAD, 30*(4), 757–766. https://doi.org/10.3233/JAD-2012-120079

Morton, V., & Torgerson, D. J. (2005). Regression to the mean: Treatment effect without the intervention. *Journal of Evaluation in Clinical Practice, 11*(1), 59–65. https://doi.org/10.1111/j.1365-2753.2004.00505.x

Munro, C. A., Winicki, J. M., Schretlen, D. J., Gower, E. W., Turano, K. A., Muñoz, B., . . . West, S. K. (2012). Sex Differences in Cognition in Healthy Elderly Individuals. *Neuropsychology, Development, and Cognition. Section B, Ageing, Neuropsychology and Cognition, 19*(6), 759–768. https://doi.org/10.1080/13825585.2012.690366

Murer, M. G., Yan, Q., & Raisman-Vozari, R. (2001). Brain-derived neurotrophic factor in the control human brain, and in Alzheimer's disease and Parkinson's disease. *Progress in Neurobiology, 63*(1), 71–124.

Nao, J., Sun, H., Wang, Q., Ma, S., Zhang, S., Dong, X., . . . Zheng, D. (2017). Adverse Effects of the Apolipoprotein E ε4 Allele on Episodic Memory, Task Switching and Gray Matter Volume in Healthy Young Adults. *Frontiers in Human Neuroscience, 11*, 346. https://doi.org/10.3389/fnhum.2017.00346

Nascimento, C. M. C., Pereira, J. R., Pires de Andrade, L., Garuffi, M., Ayan, C., Kerr, D. S., . . . Stella, F. (2015). Physical exercise improves peripheral BDNF levels and cognitive functions in mild cognitive impairment elderly with different bdnf Val66Met genotypes. *Journal of Alzheimer's Disease : JAD*, *43*(1), 81–91. https://doi.org/10.3233/JAD-140576

Neeper, S. A., Gómez-Pinilla, F., Choi, J., & Cotman, C. (1995). Exercise and brain neurotrophins. *Nature*, *373*(6510), 109. https://doi.org/10.1038/373109a0

Nelson, M. E., Rejeski, W. J., Blair, S. N., Duncan, P. W., Judge, J. O., King, A. C., . . . Castaneda-Sceppa, C. (2007). Physical activity and public health in older adults: Recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation*, *116*(9), 1094–1105. https://doi.org/10.1161/CIRCULATIONAHA.107.185650

Noack, H., Lövdén, M., Schmiedek, F., & Lindenberger, U. (2009). Cognitive plasticity in adulthood and old age: Gauging the generality of cognitive intervention effects. *Restorative Neurology and Neuroscience*, *27*(5), 435–453. https://doi.org/10.3233/RNN-2009-0496

Northey, J. M., Cherbuin, N., Pumpa, K. L., Smee, D. J., & Rattray, B. (2018). Exercise interventions for cognitive function in adults older than 50: A systematic review with meta-analysis. *British Journal of Sports Medicine*, *52*(3), 154–160. https://doi.org/10.1136/bjsports-2016-096587

O'Hara, R., Brooks, J. O. [John], Friedman, L. [Leah], Schröder, C. M., Morgan, K. S., & Kraemer, H. C. (2007). Long-term effects of mnemonic training in community-dwelling older adults. *Journal of Psychiatric Research*, *41*(7), 585–590. https://doi.org/10.1016/j.jpsychires.2006.04.010

O'Kusky, J., & Ye, P. (2012). Neurodevelopmental effects of insulin-like growth factor signaling. *Frontiers in Neuroendocrinology*, *33*(3), 230–251. https://doi.org/10.1016/j.yfrne.2012.06.002

Oswald, W. D., Gunzelmann, T., Rupprecht, R., & Hagen, B. (2006). Differential effects of single versus combined cognitive and physical training with older adults: The SimA study in a 5-year perspective. *European Journal of Ageing*, *3*(4). https://doi.org/10.1007/s10433-006-0035-z

Papp, K. V., Walsh, S. J., & Snyder, P. J. (2009). Immediate and delayed effects of cognitive interventions in healthy elderly: A review of current literature and future directions. *Alzheimer's & Dementia : the Journal of the Alzheimer's Association*, *5*(1), 50–60. https://doi.org/10.1016/j.jalz.2008.10.008

Park, Ryu, S.‐H., Yoo, Y., Yang, J.‐J., Kwon, H., Youn, J.‐H., . . . Lee, J.‐Y. [Jun-Young] (2018). Neural predictors of cognitive improvement by multi-strategic memory training based on metamemory in older adults with subjective memory complaints. *Scientific Reports*, *8*(1), 1095. https://doi.org/10.1038/s41598-018-19390-2

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: Ageing and neurocognitive scaffolding. *Annual Review of Psychology*, *60*, 173–196. https://doi.org/10.1146/annurev.psych.59.103006.093656

Pascual-Leone, A., Freitas, C., Oberman, L., Horvath, J. C., Halko, M., Eldaief, M., . . . Rotenberg, A. (2011). Characterizing brain cortical plasticity and network dynamics across the age-span in health and disease with TMS-EEG and TMS-fMRI. *Brain Topography*, *24*(3-4), 302–315. https://doi.org/10.1007/s10548-011-0196-8

Pashler, H., & Wagenmakers, E.‐J. (2012). Editors' Introduction to the Special Section on Replicability in Psychological Science: A Crisis of Confidence? *Perspectives on Psychological Science : a Journal of the Association for Psychological Science*, *7*(6), 528–530. https://doi.org/10.1177/1745691612465253

Pedersen, B. K. (2006). The anti-inflammatory effect of exercise: Its role in diabetes and cardiovascular disease control. *Essays in Biochemistry*, *42*, 105–117. https://doi.org/10.1042/bse0420105

Peters, R. (2006). Ageing and the brain. *Postgraduate Medical Journal*, *82*(964), 84–88. https://doi.org/10.1136/pgmj.2005.036665

Petrelli, A., Kaesberg, S. [Stephanie], Barbe, M. T. [Michael], Timmermann, L. [Lars], Fink, G. R. [Gereon], Kessler, J. [Josef], & Kalbe, E. [Elke] (2014). Effects of cognitive training in Parkinson's disease: A randomized controlled trial. *Parkinsonism & Related Disorders*, *20*(11), 1196–1202. https://doi.org/10.1016/j.parkreldis.2014.08.023

Petrelli, A., Kaesberg, S., Barbe, M. T., Timmermann, L., Rosen, J. B., Fink, G. R., . . . Kalbe, E. (2015). Cognitive training in Parkinson's disease reduces cognitive decline in the long term. *European Journal of Neurology*, *22*(4), 640–647. https://doi.org/10.1111/ene.12621

Posner, M. I. (2011). *Cognitive neuroscience of attention*: Guilford Press.

Prochaska, J. J. [Judith], Velicer, W. F., Nigg, C. R., & Prochaska, J. O. [James] (2008). Methods of quantifying change in multiple risk factor interventions. *Preventive Medicine*, *46*(3), 260–265. https://doi.org/10.1016/j.ypmed.2007.07.035

Rahe, J., Becker, J., Fink, G. R. [Gereon], Kessler, J. [Josef], Kukolja, J., Rahn, A., . . . Kalbe, E. [Elke] (2015). Cognitive training with and without additional physical activity in healthy older adults: Cognitive effects, neurobiological mechanisms, and prediction of training success. *Frontiers in Ageing Neuroscience*, *7*, 187. https://doi.org/10.3389/fnagi.2015.00187

Rapp, P. R., & Amaral, D. G. (1992). Individual differences in the cognitive and neurobiological consequences of normal ageing. *Trends in Neurosciences*, *15*(9), 340–345.

Raz, N., & Rodrigue, K. M. (2006). Differential ageing of the brain: Patterns, cognitive correlates and modifiers. *Neuroscience and Biobehavioral Reviews*, *30*(6), 730–748. https://doi.org/10.1016/j.neubiorev.2006.07.001

Rebok, G. W., Carlson, M. C., & Langbaum, J. B. S. (2007). Training and maintaining memory abilities in healthy older adults: Traditional and novel approaches. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *62 Spec No 1*, 53–61.

Rebok, G. W., Langbaum, J. B. S., Jones, R. N. [Richard N.], Gross, A. L., Parisi, J. M., Spira, A. P., . . . Brandt, J. (2013). Memory training in the ACTIVE study: How much is needed and who benefits? *Journal of Ageing and Health*, *25*(8 Suppl), 21S-42S. https://doi.org/10.1177/0898264312461937

Reuter-Lorenz, P. A. [Patricia A.], & Park, D. C. (2014). How does it STAC up? Revisiting the scaffolding theory of ageing and cognition. *Neuropsychology Review*, *24*(3), 355–370. https://doi.org/10.1007/s11065-014-9270-9

Riley, R. D., Hayden, J. A. [Jill A.], Steyerberg, E. W., Moons, K. G. M., Abrams, K., Kyzas, P. A., . . . Hemingway, H. (2013). Prognosis Research Strategy (PROGRESS) 2: Prognostic factor research. *PLoS Medicine, 10*(2), e1001380. https://doi.org/10.1371/journal.pmed.1001380

Riley, R. D., Moons, K. G. M., Snell, K. I. E., Ensor, J., Hooft, L., Altman, D. G., . . . Debray, T. P. A. (2019). A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ (Clinical Research Ed.), 364*, k4597. https://doi.org/10.1136/bmj.k4597

Roenker, D. L., Cissell, G. M., Ball, K. K. [Karlene K.], Wadley, V. G., & Edwards, J. D. (2003). Speed-of-processing and driving simulator training result in improved driving performance. *Human Factors*, *45*(2), 218–233. https://doi.org/10.1518/hfes.45.2.218.27241

Roheger, M., Meyer, J., Kessler, J. [Josef], & Kalbe, E. [Elke] (2019). Predicting short- and long-term cognitive training success in healthy older adults: Who benefits? *Neuropsychology, Development, and Cognition. Section B, Ageing, Neuropsychology and Cognition*, 1–19. https://doi.org/10.1080/13825585.2019.1617396

Rosi, A., Del Signore, F., Canelli, E., Allegri, N., Bottiroli, S., Vecchi, T., & Cavallini, E. (2018). The effect of strategic memory training in older adults: Who benefits most? *International Psychogeriatrics*, *30*(8), 1235–1242. https://doi.org/10.1017/S1041610217002691

Rouse, B., Chaimani, A., & Li, T. [Tianjing] (2017). Network meta-analysis: An introduction for clinicians. *Internal and Emergency Medicine*, *12*(1), 103–111. https://doi.org/10.1007/s11739-016-1583-7

Salthouse, T. A. (2013). Effects of age and ability on components of cognitive change. *Intelligence*, *41*(5), 501–511. https://doi.org/10.1016/j.intell.2013.07.005

Sandberg, P., Rönnlund, M., Derwinger-Hallberg, A., & Stigsdotter Neely, A. (2016). Memory plasticity in older adults: Cognitive predictors of training response and maintenance following learning of number-consonant mnemonic. *Neuropsychological Rehabilitation*, *26*(5-6), 742–760. https://doi.org/10.1080/09602011.2015.1046459

Scarmeas, N., & Stern, Y. (2003). Cognitive reserve and lifestyle. *Journal of Clinical and Experimental Neuropsychology*, *25*(5), 625–633. https://doi.org/10.1076/jcen.25.5.625.14576

Schaie, K. W. [K. W.] (1993). The Seattle Longitudinal Study: A thirty-five-year inquiry of adult intellectual development. *Zeitschrift Fur Gerontologie*, *26*(3), 129–137.

Schaie, K. W. [K. W.], & Willis, S. L. (2010). The Seattle Longitudinal Study of Adult Cognitive Development. *ISSBD Bulletin*, *57*(1), 24–29.

Schubert, T., Strobach, T., & Karbach, J. (2014). New directions in cognitive training: On methods, transfer, and application. *Psychological Research*, *78*(6), 749–755. https://doi.org/10.1007/s00426-014-0619-8

Shatil, E. (2013). Does combined cognitive training and physical activity training enhance cognitive abilities more than either alone? A four-condition randomized controlled trial among healthy older adults. *Frontiers in Ageing Neuroscience*, *5*, 8. https://doi.org/10.3389/fnagi.2013.00008

Shin, E., Lee, H. [Hunjae], Yoo, S.‑A., & Chong, S. C. (2015). Training improves the capacity of visual working memory when it is adaptive, individualized, and targeted. *PLoS ONE*, *10*(4), e0121702. https://doi.org/10.1371/journal.pone.0121702

Silverman, I., Kastuk, D., Choi, J., & Phillips, K. (1999). Testosterone levels and spatial ability in men. *Psychoneuroendocrinology*, *24*(8), 813–822.

Simons, D. J., Boot, W. R., Charness, N., Gathercole, S. E., Chabris, C. F., Hambrick, D. Z., & Stine-Morrow, E. A. L. (2016). Do "Brain-Training" Programs Work? *Psychological Science in the Public Interest : a Journal of the American Psychological Society*, *17*(3), 103–186. https://doi.org/10.1177/1529100616661983

Smith, G. E. (2016). Healthy cognitive ageing and dementia prevention. *The American Psychologist*, *71*(4), 268–275. https://doi.org/10.1037/a0040250

Smith, G. E., Housen, P., Yaffe, K., Ruff, R., Kennison, R. F., Mahncke, H. W., & Zelinski, E. M. (2009). A cognitive training program based on principles of brain plasticity: Results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study. *Journal of the American Geriatrics Society*, *57*(4), 594–603. https://doi.org/10.1111/j.1532-5415.2008.02167.x

Smoleń, T., Jastrzebski, J., Estrada, E., & Chuderski, A. (2018). Most evidence for the compensation account of cognitive training is unreliable. *Memory & Cognition*, *46*(8), 1315–1330. https://doi.org/10.3758/s13421-018-0839-z

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G. F., Casini, A., & Macchi, C. (2011). Physical activity and risk of cognitive decline: A meta-analysis of prospective studies. *Journal of Internal Medicine*, *269*(1), 107–117. https://doi.org/10.1111/j.1365-2796.2010.02281.x

Spector-Mersel, G. (2006). Never-ageing Stories: Western Hegemonic Masculinity Scripts. *Journal of Gender Studies*, *15*(1), 67–82. https://doi.org/10.1080/09589230500486934

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet. Neurology*, *11*(11), 1006–1012. https://doi.org/10.1016/S1474-4422(12)70191-6

Sturm, W., Herrmann, M., & Münte, T. F. (Eds.). (2009). *Lehrbuch der klinischen Neuropsychologie: Grundlagen, Methoden, Diagnostik, Therapie* (2. Auflage). Heidelberg: Spektrum Akademischer Verlag. Retrieved from http://deposit.d-nb.de/cgi-bin/dokserv?id=2992285&prov=M&dok_var=1&dok_ext=htm

Tatti, E., Rossi, S., Innocenti, I., Rossi, A., & Santarnecchi, E. (2016). Non-invasive brain stimulation of the ageing brain: State of the art and future perspectives. *Ageing Research Reviews*, *29*, 66–89. https://doi.org/10.1016/j.arr.2016.05.006

Teixeira-Santos, A. C., Moreira, C. S., Magalhães, R., Magalhães, C., Pereira, D. R., Leite, J., . . . Sampaio, A. (2019). Reviewing working memory training gains in healthy older adults: A meta-analytic review of transfer for cognitive outcomes. *Neuroscience and Biobehavioral Reviews*, *103*, 163–177. https://doi.org/10.1016/j.neubiorev.2019.05.009

Terry, R. D. (2000). Cell death or synaptic loss in Alzheimer disease. *Journal of Neuropathology and Experimental Neurology*, *59*(12), 1118–1119.

Terry, R. D., & Katzman, R. (2001). Life span and synapses: Will there be a primary senile dementia? *Neurobiology of Ageing*, *22*(3), 347-8; discussion 353-4.

Unverzagt, F. W., Smith, D. M., Rebok, G. W., Marsiske, M., Morris, J. N., Jones, R., . . . Tennstedt, S. L. (2009). The Indiana Alzheimer Disease Center's Symposium on Mild Cognitive Impairment. Cognitive Training in Older Adults: Lessons from the ACTIVE Study. *Current Alzheimer Research*, *6*(4), 375–383.

Van Praag, H. (2009). Exercise and the brain: Something to chew on. *Trends in Neurosciences*, *32*(5), 283–290. https://doi.org/10.1016/j.tins.2008.12.007

Verhaeghen, P., Marcoen, A., & Goossens, L. (1992). Improving memory performance in the aged through mnemonic training: A meta-analytic study. *Psychology and Ageing*, *7*(2), 242–251.

Voss, M. W., Erickson, K. I. [Kirk I.], Prakash, R. S., Chaddock, L., Kim, J. S., Alves, H., . . . Kramer, A. F. (2013). Neurobiological markers of exercise-related brain plasticity in older adults. *Brain, Behavior, and Immunity*, *28*, 90–99. https://doi.org/10.1016/j.bbi.2012.10.021

West, R. L., & Hastings, E. C. (2011). Self-regulation and recall: Growth curve modeling of intervention outcomes for older adults. *Psychology and Ageing*, *26*(4), 803–812. https://doi.org/10.1037/a0023784

Whitlock, L. A., McLaughlin, A. C., & Allaire, J. C. (2012). Individual differences in response to cognitive training: Using a multi-modal, attentionally demanding game-based intervention for older adults. *Computers in Human Behavior*, *28*(4), 1091–1096. https://doi.org/10.1016/j.chb.2012.01.012

WHO (Ed.). (2010). World Health Report 2010: Global Recommendations on Physical Activity for Health. [Special issue]. Switzerland: WHO.

Willis, S. L., Tennstedt, S. L., Marsiske, M., Ball, K., Elias, J., Koepke, K. M., . . . Wright, E. (2006). Long-term Effects of Cognitive Training on Everyday Functional Outcomes in Older Adults. *JAMA : the Journal of the American Medical Association*, *296*(23), 2805–2814. https://doi.org/10.1001/jama.296.23.2805

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.‐O., . . . Petersen, R. C. (2004). Mild cognitive impairment--beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine*, *256*(3), 240–246. https://doi.org/10.1111/j.1365-2796.2004.01380.x

Wisdom, N. M., Callahan, J. L., & Hawkins, K. A. (2011). The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. *Neurobiology of Ageing*, *32*(1), 63–74. https://doi.org/10.1016/j.neurobiolageing.2009.02.003

Zhu, X., Yin, S., Lang, M., He, R., & Li, J. (2016). The more the better? A meta-analysis on effects of combined cognitive and physical intervention on cognition in healthy older adults. *Ageing Research Reviews*, *31*, 67–79. https://doi.org/10.1016/j.arr.2016.07.003

Ziegler, A. N., Levison, S. W., & Wood, T. L. (2015). Insulin and IGF receptor signalling in neural-stem-cell homeostasis. *Nature Reviews. Endocrinology*, *11*(3), 161–170. https://doi.org/10.1038/nrendo.2014.208

# 6. Acknowledgements

Mein besonderer Dank gilt meiner Betreuerin Elke Kalbe für die wunderbare Betreuung während der letzten Jahre, dem schönen Arbeitsumfeld und die stets produktive und gute Zusammenarbeit. Außerdem möchte ich meiner Betreuerin Hilde Haider herzlich für die stete Unterstützung und ihr Feedback danken, das mich immer zum weiteren Nachdenken angeregt hat.

Mein weiterer Dank gilt meinen Kolleg*innen der Abteilung Medizinische Psychologie | Neuropsychologie & Gender Studies für viele spannende Gespräche, gesellige Mittagspausen und der Hilfe bei dieser Arbeit. Ganz besonders möchte ich „dem Büro dahinten" danken: Anja Ophey, Hannah Liebermann-Jordanidis und Fabian Krohm, für die ganze Unterstützung (sowohl inhaltlich als auch emotional) während der letzten Jahre und vor allem Wochen beim Fertigstellen dieser Arbeit, ihrer guten Laune, und ihrer Fähigkeit mein zeitweiliges Chaos und meine Cola-Sucht auszuhalten. Anja, Dir möchte ich besonders danken: einmal dafür, dass du diese Arbeit Korrektur gelesen hast, aber auch und vor allem dafür, dass wir in den letzten Jahren so vieles geteilt haben: Höhen und Tiefen, Wünsche und Hoffnungen, Erinnerungen an gemeinsame Konferenzen und Ausflüge - und zeitweise auch unseren Schreibtisch.

Mein Dank gilt außerdem der Friedrich-Ebert-Stiftung, für ihre finanzielle als auch ideelle Unterstützung meiner Promotion, für die vielen spannenden Seminare, die ich besuchen durfte, und die interessanten Menschen und Geschichten, die ich kennenlernen konnte.

Zuletzt möchte ich mich bei meinen Freund*innen (vor allem Julia Meisters für das Korrekturlesen der Arbeit) und meiner Familie bedanken: Ohne Euch und Eure Unterstützung wäre diese Arbeit nicht möglich gewesen.