Cognitive flexibility training in healthy aging

A game a day does not keep the doctor away

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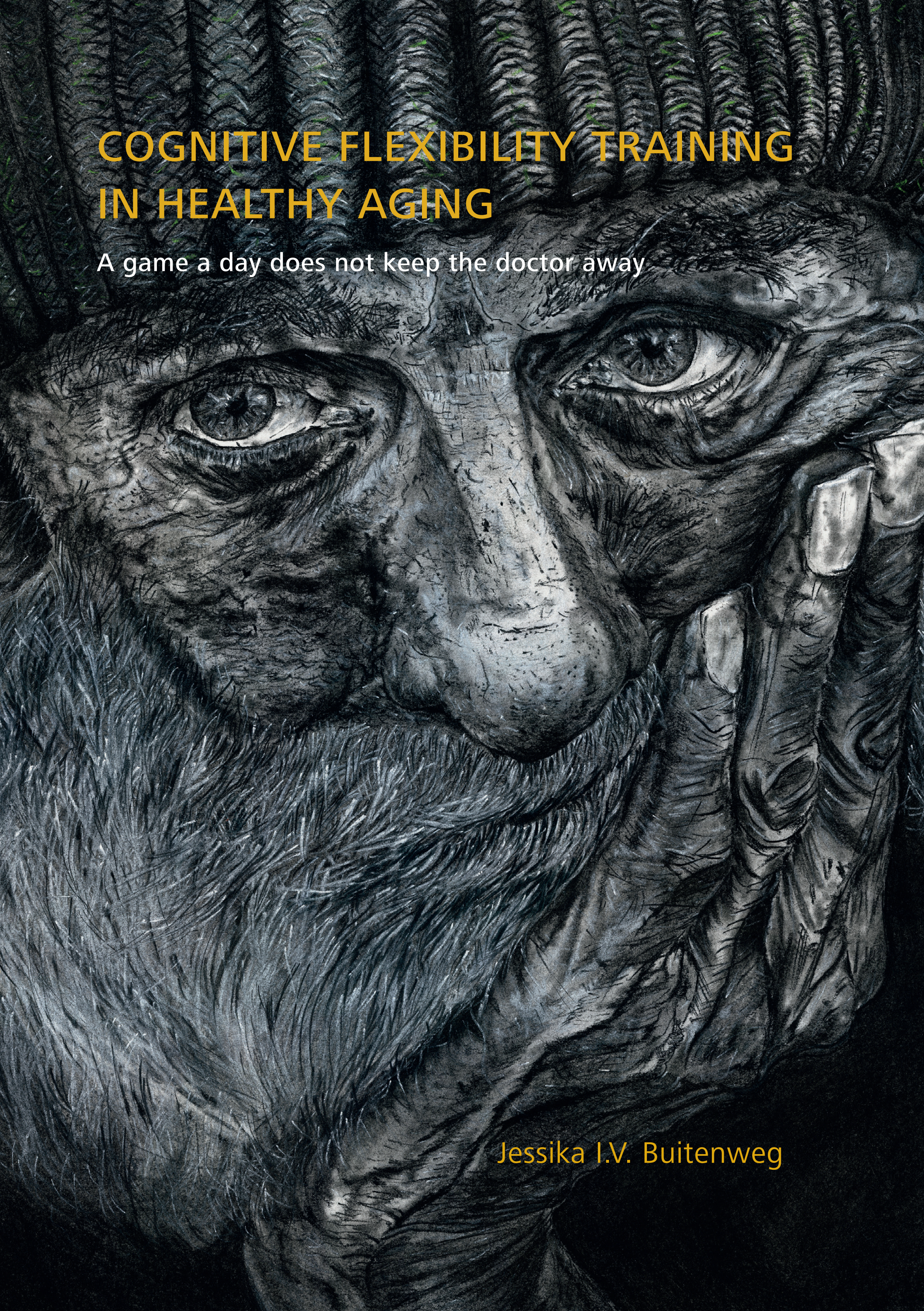

COGNITIVE FLEXIBILITY TRAINING IN HEALTHY AGING

A game a day does not keep the doctor away

Jessika I.V. Buitenweg

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Cognitive flexibility training in healthy aging -
A game a day does not keep the doctor away

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Faculteit der Maatschappij- en Gedragswetenschappen

Aging is an extraordinary process whereby you become the person you always should have been

(David Bowie)

CONTENTS

Chapter 1

General Introduction

> *Johan is a 69-year-old ex-schoolteacher. He has enjoyed the first few years of retirement, but after visiting a number of long-lost relatives and spending more time on his hobby of painting, he finds himself growing a bit bored. Besides, he notices that his thinking skills are not as they used to be. He loses his concentration more often, forgets words and appointments and struggles to keep up with the conversation when talking to ex-colleagues. At first, he worries that he is starting to develop dementia, and schedules a meeting with his general practitioner. She runs a few tests, and reassures him that there is nothing to worry about: Johan is only experiencing the effects of normal aging. Nonetheless, he is irritated by the changes and is determined to take action to keep his mind sharp.*

We often generally associate old age with increased wisdom, life experience and acquiescence. Yet, once we reach a respectable age, we might find, much like Johan, that elderly life is burdened by failures in physical and mental functions and subsequent concerns about possible permanent impairments. This thesis serves to answer a number of questions pertaining to a possible contribution in delaying, compensating or even reversing the loss of functioning underlying these fears. After treating each of these questions in the coming chapters we will once more regard Johan, and individuals like him, in the light of our findings, and offer them advice based on the current state of affairs.

As a result of better overall hygiene and important developments in healthcare, life expectancy in the Western world has been growing since the early 1900’s. Vaccination, medication, surgical procedures and other scientific and medical breakthroughs have and still continue to increase longevity. Due to the decline in death rate as well as in birth rate, the proportion of older adults among the world’s population is rapidly expanding. Whereas in 2017, 24% of European populations consisted of people older than 60, in 2050 this number is expected to rise to 35% (United Nations, 2017).

Yet, while in most corners of the world people are living longer lives, enjoying their grandchildren, exploring the globe, or (re)discovering old or new hobbies, many of them fear the looming decline of cognitive functions and the possibility of debilitation by progressive aging diseases such as Alzheimer’s or Parkinson’s disease (Corner & Bond, 2004; Pan et al., 2014). Symptoms of age-related neurological diseases worsen over time, leading to a decline in quality of life and interfering with daily functioning, eventually rendering one fully dependent on others. Although the majority of older adults will not be diagnosed with one these progressive diseases, many will at some point experience cognitive loss through the process of normal aging.

In this thesis, I aim to explore whether regular use of an *adaptive cognitive flexibility training* can be effective in preserving or reclaiming cognitive and subjective performance in the older population. In the following sections, I will briefly introduce and discuss the main patterns of age-related decline pertaining to subjective complaints, cognitive (dys)function, and neural efficiency (deterioration in brain structure and connectivity, and reduced neurotransmission), respectively. This will be followed by a brief overview of, first, models and theories capturing these changes, and second, consequences of these changes for individuals and for society. Finally, I will briefly discuss the issue of preserved neural plasticity, and present an overview of the types of (preventative) interventions that are prevalent in the current literature, with some emphasis on brain training procedures, and on criteria for these procedures to be meaningfully employed in experimental research. This chapter will be closed by a summary of the aims of the present thesis work, and an outline of the thesis as a whole.

Subjective complaints of daily-life functioning

With increasing cognitive decline, older individuals become more aware of the transient nature of the human body and their own mental capacities. Although older adults often report to be more emotionally stable and to suffer less from external stressors compared to middle-aged adults (Brose et al., 2013), deterioration of cognitive abilities can provide another source of stress. Many individuals worry about declining memory functions and impending dementia, and some will experience increased anxiety when confronted with losses in memory (Sinoff & Werner, 2003). Despite some continuing to actively seek out social engagement and activities, others find interactions with friends becoming much more sparse, and with the loss in friendly and societal relationships people's sense of purpose may fade. Subsequent loneliness and isolation are common phenomena in old age, leading to impaired quality of life, depression, and further reduction of mental activity.

Although evidently, quantifiable cognitive decline can be a risk factor for further impairment, the presence of subjective complaints of cognitive failure in daily activities also is an important predictor of the longitudinal course of memory decline over time (Hohman et al., 2011). Additionally, the prevalence of both anxiety and depression are found to be positively correlated with progressing cognitive decline, posing as a risk for mild cognitive impairment and dementia (Bierman et al., 2007; Sinoff & Werner, 2003). In other words, presence of subjectively reported symptoms can also be a relevant indication of future memory loss and cognitive problems. Collecting frequent reports of subjective complaints therefore seems warranted to depict gradual decline over time before objective cognitive changes would become visible.

Cognitive Dysfunction

In healthy aging, whether largely unnoticed or dramatically present, some cognitive functions will slowly start to decline. As mentioned before, many will complain about their short-term memory failing, while some find it harder to concentrate on a task or notice that they can no longer perform more than one central task as a time. Other changes are so subtle they are not likely to be noticed on a day-to-day basis, such as changes in speed of processing or reaction time. As such, there is considerable interindividual variation in the rate and fashion in which functions deteriorate. Several studies link these age-related declines to deficits in executive control functions, such as the ability to inhibit inappropriate responses or irrelevant information or to maintain and manipulate information in working memory (Fisk & Sharp, 2004; Zimprich & Kurtz, 2013). As these functions rely especially on the frontostriatal pathways, weakened by aging processes early on, deficits in these executive functions are thought to underlie the changes noticed by older individuals in day-to-day life. One frequently used classification of executive functions is the three-component model by Miyake et al. (2000) which separates the functions into the three domains of shifting, inhibition and updating. As these functions support our day-to-day activities, individuals might gradually experience more difficulties in planning, multi-tasking, remembering information, and setting priorities.

Deterioration in brain structure and connectivity

Along with the decline of valuable cognitive functions, a number of neuronal changes are identified that correlate with increased age and are thought to be strongly associated with these cognitive changes. Shrinkage of cortical gray matter networks across the brain correlates with decreasing memory and executive functions (Koini et al., 2018). Volume decrease in specific subcortical structures, such as the hippocampus, are seen in healthy older individuals with memory dysfunctions (Persson et al., 2005). White matter volume declines across the whole brain (Barrick et al., 2010) but especially in anterior parts, with large individual differences in the degree of atrophy (Raz et al., 2010). Although neuronal death has long been believed to be responsible for age-related loss of volume, it is more likely to be due to shrinkage of neurons and change in dendritic systems (Freeman et al., 2008) and loss of myelinated fibers (Marner et al., 2003). Moreover, on structural MRI, white matter hyperintensities can often be seen: small lesions visible in the deep white matter and around the ventricles. Although previously thought to be a trivial occurrence in healthy aging, they are now known to be associated with higher cognitive dysfunctions and risk of stroke and dementia (Maniega et al., 2015).

Declines in neurotransmission

A number of marked changes in neurotransmission occur with increased age, that are important to note, as they explain some of the age-related dysfunctions. For instance, serotonin signal transmission is thought to be reduced due to decreases in expression of receptors and binding sites in multiple brain areas (Karrer et al., 2019; Rodriguez et al., 2012). Low levels of serotonin can have adverse effects on learning and memory (Meneses, 2015; Zhang & Stackman, 2015), anxiety (Canli & Lesch, 2007) and sleep (Melancon et al., 2014) and can pose a risk for dementia and depression (Rehman & Masson, 2001). Boosting these levels, on the other hand, has a positive effect on cognition both in healthy adults and in those suffering from Alzheimer's disease, and especially improves memory (Rodriguez et al., 2012).

Dopaminergic function has also been shown to be affected by advanced age. Although dopamine synthesis is upregulated in older adults (Berry et al., 2016) receptors density in basal ganglia is seen to decrease (Rehman & Masson, 2001). Reductions in receptor binding are demonstrated specifically in the caudate and DLPFC (Bäckman et al., 2011; Rieckmann et al., 2011), which is associated with increased interindividual variability with age (MacDonald et al., 2012). These changes in dopamine function are demonstrated to be responsible for dysfunctions dependent on frontostriatal networks, such as inhibition and flexibility deficits (Volkow et al., 1998). However, correlations with performance on (executive) functioning tasks, such as working memory and processing speed, are stronger than the relationship with age, and remain present even after age is taken into account (Bäckman et al., 2006), signifying that individual differences in striatal dopamine receptor binding predicts cognitive decline more strongly than age itself, and that dopamine dysfunctioning lies at the core of the problem of cognitive aging symptomology. Measuring internal dopamine functioning in humans remains a challenge (Berry et al., 2016). Dopaminergic binding is frequently measured with ligand-PET using radioactive tracers, though due to the invasive and costly nature of this method, recent studies have explored other means, such as spontaneous eye blink rate. This measure proves to be a good predictor of the density of striatal dopamine receptors, for instance, in individuals with dopaminergic dysfunctions such as Parkinson’s disease and schizophrenia (Deuschl & Goddemeier, 1998; Mackert et al., 1990). Yet, eye blink rate also has been shown to be a reliable measure of the link between executive control and D2 dopaminergic function (Colzato et al., 2009; Kleinsorge & Scheil, 2017) and as such, might also predict this relationship in the older population.

Models and theories of neurocognitive aging

Although large changes can be seen with aging both in the brain and in functional performance, the visible onset of decline typically varies greatly between individuals. A prominent theory explaining the different trajectories of developing age-related deterioration or clinical dementia is that of brain reserve and cognitive reserve (Stern, 2012). Brain reserve is thought to be associated with larger brain volume or number of neurons, leading to a decreased susceptibility to pathological changes, while cognitive reserve is defined as the ability to manage the use of these remaining systems using alternate mechanisms and processes to compensate for change. In other words, the degree of brain reserve denotes the threshold after which age-related changes lead to noticeable cognitive decline, while cognitive reserve defines the active ability to cope with these changes. In this way, both brain reserve and cognitive reserve offer a type of compensation for alterations brought on by aging. Higher brain- and cognitive reserve are suggested to be related to increased cognitive stimulation and challenging environments throughout life (Stern, 2009), for instance through increased mental activities and education (Valenzuela & Sachdev, 2006). Although this consequently lowered susceptibility, also known as *resilience*, is expressed as a reduction or a delay in functional decline, physical changes still occur, as can be seen in the brain. Older individuals with high reserve still show structural decline, which is, in fact, often more pronounced in high reserve individuals than in those with low reserve (Brickman et al., 2011; Liu et al., 2012; Solé-Padullés et al., 2009). Thus, when confronted with neuronal changes, it is thought that those with higher cognitive reserve learn to compensate, generally by recruiting different networks.

Several models have been construed explaining the possible underlying mechanisms of compensation. One of them is the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH), which states that different structures or neural networks are necessary in performing a task to compensate for declining brain functions (Reuter-Lorenz & Cappell, 2008). Overactivation is suggested to be the case especially at lower levels of cognitive load, as older adults need to recruit additional brain capacity compared to young to get similar performance results. For higher loads, smaller increments in activation are seen, and performance falls behind (Cappell et al., 2010; Schneider-Garces et al., 2010). For instance, Persson et al. (2005) demonstrate in a longitudinal study that individuals that have sustained greater decline in memory recruit additional frontal regions compared to older adults with less or no memory dysfunctions. As this reduction of overactivation is especially the case for individuals with additional decline, this might be indicative of a lower threshold in brain reserve. On the other hand, activation of additional brain regions has also been found to predict increased performance on a task (Heuninckx et al., 2008). Given that both improved and impaired performance is seen as a confirmation of this theory, caution about falsifiability is warranted, a concern also voiced by Jamadar (2018).

Other studies find that initially specialized structures become functional for different or multiple purposes, a trend referred to as ‘dedifferentiation’ (Goh, 2011). Dedifferentiation is considered a separate process, not based on compensatory activity. For example, when administered two distinct memory tasks, young adults preferentially use one area above the other for different tasks, whereas among older adults such differentiation is less prevalent (Dennis & Cabeza, 2011). This pattern also is mostly associated with greater decline, as shown, for instance, in a study by Voss (2008) in which higher overall gray-matter volume was associated with a lower tendency towards dedifferentiation.

A slightly different model that tries to explain the overactivation seen in aging research is the Scaffolding Theory of Aging and Cognition (STAC; Park & Reuter-Lorenz, 2009). This theory postulates that despite the adverse neurocognitive changes, many functions remain intact in aging adults. To achieve this, the brain actively reorganizes in response to the neuronal declines, in order to reinforce task performance. According to this model, a dependence on these scaffolding networks is thought to be essential for healthy aging. Evidence for this model comes from studies showing that extra, often prefrontal, activity occurs together with age-related underactivation of structures dedicated to specific functions (Davis et al., 2003). This theory also indicates that the aging brain is still capable of positive change with continuous engagement, or exposure to old or new challenges, a proposition corresponding to the concept of brain- and cognitive reserve (Stern, 2012) and emphasizing the possibility for positive change over time.

Consequences for individuals and for society

Altogether, the aging brain ultimately is a slowly deteriorating system, on neuronal, structural, and functional levels. Moreover, the majority of older adults will retire after a certain age, limiting the engagement in regular cognitive and social activities and lowering the demand on cognitive systems. This might be the case in the story of Johan at the start of this chapter, whose brain disuse may cause some of the already waning functions to worsen even further. As the percentage of older people in society is rising rapidly, so will the number of individuals with healthy aging deficits and illnesses. Geriatric care, in nursing homes or as in-home care, is provided to those no longer able to care for themselves. However, due to the growing number of aging adults, the healthcare system is being challenged. Costs have risen to an overall high that society is no longer able to finance, a shortage of staff has ensued, leaving the remaining care workers carrying an unsustainable burden, and more individuals are subject to elder neglect or –abuse. Furthermore, as a result of economic shifts, fewer people are able to take up regular care for their parents, leading to a further increase in the use of in-home care workers and placement in retirement homes. National governments have attempted to regulate the situation in geriatric care by discouraging the use of nursing homes, and urging older individuals to prolong living independently. As promising as this prospect might be, this has elicited further issues. Many older adults, even when mostly independent, feel increasingly lonely and insecure, first aid services and GP care are used extensively, and the chance of depression and other negative (mental) health outcomes is rising (Gale et al., 2017; Gonyea et al., 2018). For those suffering decreasing cognitive flexibility and memory, day-to-day chores around the house become more encumbering, and regular external care must be called upon. To this end, an imminent solution is needed to maintain cognitive functions in the aging population to extend independent, dignified life.

Preserved plasticity?

Although these statements might appear to paint a bleak picture of our society of the future, a number of possible outlooks exist, a few of which have gotten ample attention during the last decade especially. Their feasibility builds on the phenomenon of plasticity. For long, it was believed that aging brains were no longer capable of neurogenesis, the generation of new cells. Although neurogenesis does slow down with advanced age (Boldrini et al., 2018), studies now show that new neurons continue to be produced, especially in dentate gyrus and the subventricular zone of the hippocampus (Boldrini et al., 2018; Katsimpardi & Lledo, 2018). Similarly, plasticity continues to take place, first of all, as functional plasticity: the aforementioned reorganization by dedifferentiation and compensation (Park & Reuter-Lorenz, 2009). Besides this, structural plasticity can occur by learning, for instance after acquiring a new skill. Gray matter volume increases have been found in older adults after juggling training (Boyke et al., 2008) and dancing (Müller et al., 2017; Rehfeld et al., 2018) when compared to active controls. Besides, tDCS, a form of noninvasive electrical stimulation of the brain, has shown to facilitate motor learning in older adults on a task normally subject to decline (Zimerman et al., 2013). In other words, plasticity remains possible in older ages, both by direct stimulation of the brain and by learning of new skills.

Preventive interventions for preservation and recovery of cognitive functioning

In solving the dilemma of how to keep the aging population mentally fit, most studies emphasize not the learning of new skills, but rather the preservation and recovery of declining cognitive functions central to day-to-day life. Through the possibility of training-induced plasticity, older adults are offered training protocols, in order to attempt to counteract age-related cognitive decline, measured most frequently using tasks of transfer. Transfer refers to the degree to which generalisation of the trained skills occurs on untrained tasks, with near and far transfer indicating improvements on domains similar or more dissimilar to the training tasks, respectively.

A number of different possible interventions have been investigated over the years. Aerobic exercise has been demonstrated to preserve cognitive health in aging adults by improving executive functions, processing speed, and attention (Chang et al., 2015; Kaushal et al., 2018) and by increasing frontal and temporal grey- and white-matter volume (Colcombe & Kramer, 2003; Colcombe et al., 2006) and functional connectivity (Voss et al., 2010). Incorporating both physical and cognitive training into one intervention, for instance by using exergaming (Maillot et al., 2012) or cybercycling (Anderson-Hanley et al., 2012) has also been a promising way to enhance functions such as executive control and processing speed, and to affect prefrontal activation patterns (Eggenberger et al., 2016). This type of combined training has also been shown to provide a buffer for normal age-related volume decreases. For instance, after a spatial navigation training in which participants walked on a treadmill performing search tasks in a virtual environment, researchers found that hippocampal volumes remained stable, compared to an active control group in which volumes decreased (Lövdén et al., 2012).

By far the most investigated type of intervention is that directly stimulating cognitive functions, also known as brain training. Many studies attempt to generate improvement by targeting one domain of functioning, such as working memory (Buschkuehl et al., 2008; Richmond et al., 2011; Rose et al., 2015), reasoning (Willis & Caskie, 2013), speed of processing (Wolinsky et al., 2013), or long-term memory (Engvig et al., 2014). Others integrate different domains, for instance by offering game-based training (Baniqued et al., 2013; Basak et al., 2008; van Muijden et al., 2012; Nouchi et al., 2012; Toril et al., 2016). Additionally, as increasing numbers of European older adults are successfully using the Internet from their own homes (Eurostat, 2019), the use of computerized at-home interventions becomes a more likely alternative to clinician-guided clinical trials. Although these unmonitored settings can create a number of challenges, such as the inability to offer individual attention, motivation or explanation to training participants, and the likelihood that home environments might differ between participants and between sessions, computerized interventions pose a number of important advantages. For instance, besides being more time- and cost-efficient, it offers the possibility of standardizing certain elements, such as timing, and tailoring others, such as a session’s difficulty levels; individuals can keep track of their own progress and might be given a choice in the contents of a session, allowing them more control over their own mental health; and more diverse populations can be approached, i.e. to include those with physical or medical issues or those living further away.

At the same time, outcomes of brain training studies are met with some criticism. According to a number of recent meta-analyses, training studies, especially those targeting specific functions, tend to have low effect sizes and show no more than near transfer to the domains trained, even if only including studies with a minimum of 6 months (Butler et al., 2018; Martin et al., 2011; Sala & Gobet, 2018). Besides, most studies do not pay attention to risk of decline to MCI or AD or daily-life functions, limiting the studies in their external validity. Several programs are based on a small number of training sessions, and active controls are not always included (Noack et al., 2009). Lastly, transfer tasks are often reported as composite scores or are not validated, rendering comparisons between studies more difficult (Melby-Lervåg et al., 2016).

Based on these points of criticism, it seems essential to tailor future brain training programs to include this knowledge. A clear overview must be made from the training literature, listing the most fundamental components to attain higher effect sizes and sustained or far transfer. Assessment should include measures of daily life functioning, and validated, separately defined transfer tasks. Additionally, training programs need to be multimodal, engaging a variety of domains, and should always include an active control condition.

AIM AND OUTLINE OF THIS THESIS

The aim of this thesis was, first of all, to assess findings from previous training studies to evaluate the most effective elements of training; second, to use this information to develop an evidence-based, adaptive, multimodal cognitive flexibility training tool for online at-home use in older adults; third, to thoroughly investigate its efficacy in this population on a large range of cognitive functions such as executive functioning, processing- and psychomotor speed, and planning, and on subjective performance, such as subjective cognitive failures, executive dysfunctioning and depressive symptoms. Lastly, we intended to examine the connection between cognitive functioning and eye blink rate, an indirect measure of dopaminergic function, in older adults, as well as study whether benefit from training is dependent on this measure.

In **chapter 2**, we review the evidence behind cognitive training, which appears to be abundant, though effects are not solid and longitudinally sustained effects appear few and inconsistent. We included research studies published before 2012. We present support for the elements necessary to bring about effective transfer and maintenance of functions in future training studies, including adding elements of flexibility and novelty to cognitive interventions, and providing a diverse set of tasks engaging multiple cognitive functions. We also emphasize the need to design interventions to be adaptive to the individual level and speed of learning, such that every person is challenged to the maximum of their abilities. We incorporated this information to develop the Training Project Amsterdam Seniors and Stroke (TAPASS), a randomized controlled trial in cooperation with a study in stroke survivors. In **chapter 3,** we report on the behavioral results of this training, a game-based 12-week intervention with frequent sessions and flexible, adaptive, novel training tasks. Transfer effects were measured in healthy older adults before, during and after the training, on tasks of executive control, processing speed, verbal long term memory, verbal fluency, planning and reasoning. In **chapter 4**, we present the results of TAPASS on subjective mental functioning: cognitive failures and executive dysfunctioning, symptoms of depression and anxiety, everyday functioning, and quality of life, measured in healthy older adults before and after the training and compared to an active control condition. Proxy ratings on executive dysfunctioning and cognitive failures are also reported. **Chapter 5** describes our use of spontaneous eye blink rate to associate striatal dopamine with executive functioning and trainability in healthy older adults. We measured eye blink rate along with several measures of executive functioning: task switching, updating, and inhibition, before and after our cognitive training. We report the relationship between these measures, as well as on predictability of training benefit using individual differences in striatal D2. Finally, in **chapter 6**, we present a critical discussion of this thesis and cognitive interventions as a whole and discuss implications and recommendations for future studies.

Chapter 2

Brain training in progress: a review of trainability in healthy seniors

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Based on:

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ABSTRACT

The cognitive deterioration associated with aging is accompanied by structural alterations and loss of functionality of the frontostriatal dopamine system. The question arises how such deleterious cognitive effects could be countered. Brain training, currently highly popular among young and old alike, promises that users will improve on certain neurocognitive skills, and this has indeed been confirmed in a number of studies. Based on these results, it seems reasonable to expect beneficial effects of brain training in the elderly as well. A selective review of the existing literature suggests, however, that the results are neither robust nor consistent, and that transfer and sustained effects thus far appear limited. Based on this review, we argue for a series of elements that hold potential for progress in successful types of brain training: (i) including flexibility and novelty as features of the training, (ii) focusing on a number of promising, yet largely unexplored domains, such as decision-making and memory strategy training, and (iii) tailoring the training adaptively to the level and progress of the individual. We also emphasize the need for covariance-based MRI methods in linking structural and functional changes in the aging brain to individual differences in neurocognitive efficiency and trainability in order to further uncover the underlying mechanisms.

INTRODUCTION

Given the continuously growing number of elderly and their increasing longevity expectation, there is a pressing need to prolong independent functioning and to sustain quality of life by delaying the effects of cognitive decline. Human aging is typically associated with a deterioration of cognitive functioning, which is seen in multiple domains, including memory, decision-making, and cognitive control (Brown & Ridderinkhof, 2009; Fisk & Sharp, 2004; Luo & Craik, 2008). Decline is associated with shrinkage of prefrontal cortex, hippocampus, and basal ganglia (Raz et al., 2005) and alterations in their structural connectivity (Madden et al., 2009; O'Sullivan et al., 2001), along with a decrease in synthesis and binding of dopamine, serotonin and acetylcholine (Bäckman et al., 2006; Schliebs & Arendt, 2011; Volkow et al., 1998; Wang et al., 1995; Wang et al., 1998). Together, these structural changes cause neuromodulator levels to drop, affecting important functional pathways, principally in striatal and frontostriatal areas (Bäckman et al., 2006).

A number of interventions have been suggested to slow down this decline. Offering a motivational incentive has been demonstrated to have beneficial effects on cognitive performance (Harsay et al., 2010), and individual differences in this benefit are related to several frontostriatal white matter pathways (Harsay et al., 2011). Aerobic exercise has also been shown to aid in maintaining cognitive health by reducing age-related loss and adding to volume of grey and white matter in frontal and temporal cortices (Colcombe et al., 2003; Colcombe et al., 2006). Recent DTI studies suggest a relation between exercise and increased FA in white matter tracts (Marks et al., 2007; Voss et al., 2010). Another set of interventions concerns mental stimulation, collectively known as brain training: activities intended to challenge cognitive abilities and induce learning. Unfortunately, the many different brain training studies employ a range of varying methods and definitions, participants are not consistently subjected to tests of transfer and long-term retention, and evidence pointing to the trainings' effectivity is inconsistent. These limitations notwithstanding, brain training is practiced by elderly on a large scale.

An important concept in the realm of cognitive training is that of transfer, the degree to which the learned skill is displayed in a different context, with near and far transfer referring to generalization of training effects to domains proximal to or more distant from the trained skill, respectively. Recent reviews of the current brain training literature on this topic conclude that training programs generally fail to display fundamental transfer, with the exception of process-based cognitive control tasks (Lustig et al., 2009; Noack et al., 2009; Papp et al., 2009). They comment on the limited methodology and arbitrary assignment of transfer tasks as either near or far, which make it difficult to draw conclusions on transferability. Furthermore, many studies do not make use of active controls, thus limiting the generalizability of results. Noack et al. (2009) also note that, given the fact that training programs mostly consist of no more than a few sessions of training, the transfer found in these cases is unlikely to be mediated by neural plasticity. In working-memory training, transfer effects are also seen to be small or nonexistent (Dahlin et al., 2009), although long-term sustained gains are reported at least for the task trained. Concerning memory, Hertzog et al. (2008) proposed that interventions should engage multiple mechanisms closely related to executive control- and other functions used by elderly on various settings in daily life.

Although a good number of articles have been written reviewing some important domains in brain training literature, we feel the need to add to the current literature by drawing attention to a number of largely unexplored perspectives, in addition to emphasizing a few promising components that may make up an effective intervention. Given the current state of brain training research in elderly, the negative overall outlook notwithstanding, a number of aspects may potentially contribute to success of future studies, which motivates our discussion of these issues in the current article. First, much attention has been paid to interventions involving cognitive control, some of which (in particular those involving cognitive flexibility) seem very promising. A systematic analysis could therefore be useful in generating an overview of the types of tasks that result in meaningful transfer and long-term retention. Second, several avenues that might well prove to be effective have yet been largely ignored in brain training research. These include decision-making and -learning, which are affected by old age and could potentially benefit from training; novelty, which prepares the neuronal system for learning and could enhance ensuing synaptic plasticity; and memory strategy training, which could transcend the memory domain and lead to far transfer. Finally, and importantly, we believe future studies can profit from a stronger emphasis on inter-individual differences in trainability. The current literature largely fails to take such individual differences and their underlying determinants into consideration. Given the massive individual differences in performance and the rate of neurocognitive decline among the elderly population, future studies thus may benefit from incorporating individual fine-tuning and adaptation into the training programs, in particular from focusing on who does and who does not benefit from a given training program, and from using neuroimaging to connect inter-individual differences in performance to perceivable differences in brain structure as well as functional connectivity and/or activation.

We will first review the current evidence on training of executive functions, arguing that persistent training of cognitive control functions can, under certain conditions, enhance performance and lead to near and far transfer. We then focus on some additional perspectives which have not yet or only modestly been implemented as an intervention, but seem to hold promise in enhancing functioning. Finally, we address the importance of recognizing the inter-individual differences in brain and behavior between elderly and its impact on cognitive training possibilities.

TRAINING EXECUTIVE FUNCTIONS

Executive functioning concerns the regulation and control of goal-directed actions. Due to the large functional dependence on prefrontal cortex and basal ganglia (Ridderinkhof et al., 2004; Ridderinkhof et al., 2011), functions of executive control are especially prone to decline in old age (Treitz et al., 2007). It is thus reasonable to assume that training of executive functions can benefit elderly in daily life performance. This might pertain especially to tasks engaging cognitive flexibility (Buchler et al., 2008; Karbach & Kray, 2009), in other words, tasks that strengthen the general ability to adapt one's responses to the demand of the current situation and stimulate creative, novel thought. For this reason we focus strongly on executive functioning training, notably those domains that hold greatest promise in inducing flexibility. The executive functions are often divided, according to a widely adopted classification model based on latent-factor analysis by Miyake and colleagues (2000), into three separate domains of functioning: shifting, updating, and inhibition, which we will follow here.

Shifting

Shifting involves the flexibility to switch one's attention and one's actions between relevant tasks or subtasks, thus also dealing with interference. This is often symbolized by task switching and by multitasking. In task switching a switch is made between different aspects or properties of a stimulus, different task rules, or different effectors, frequently relying on retrieval from working memory. Multitasking (dual-tasking) requires subjects to perform several tasks concurrently, putting a strain on information processing resources.

Task switching

Studies of cognitive switching commonly report a decline in older age (Wecker et al., 2005), although there is also some evidence to the contrary (Della Sala et al., 2010; Logie et al., 2004). Age effects have been seen to diminish after extensive training on a switching task (Kramer et al., 1999), even when requiring switching between 4 different tasks (Buchler et al., 2008). Kray and Lindenberger (2000) differentiate between mixing and switch costs. Switch costs refer to increased latencies and error rates on switch trials compared to non-switch trials. Mixing costs are slower or more error-prone responses occurring when performing non-switch trials in the context of a switch task compared to the context of a single task. Although both types of costs can be reduced by training, mixing costs are suggested to be more compromised by aging than switch costs (Kray et al., 2008; Kray & Lindenberger, 2000), implying that aging especially affects the ability to keep multiple sets in working memory rather than making the shift itself. At the same time, mixing costs are also most sensitive to improvement (Kray et al., 2008; Strobach et al., 2012). Kray et al. (2008) found that when subjects verbalized their task cues before shifting to a different task, a reduction of mixing costs was seen especially in older adults compared to younger adults, whereas switch costs did not benefit from verbalizations.

Not only does training in task switching demonstrate enhancement on the task itself, recent studies also show the possibility of near and far transfer. Elderly who have grown up as bilinguals, thus constantly needing to switch between the two languages during their lifetime, are found to have an advantage in inhibitory control compared to monolingual elderly (Bialystok et al., 2004; Bialystok et al., 2006). Older adults who received training in task switching showed a reduction in mixing and switch costs on a similar switch task (Karbach & Kray, 2009; Karbach et al., 2010), but also displayed reduced interference effects on a Stroop task, and improved spatial and verbal working memory and fluid intelligence, in contrast to baseline and to elderly subjects receiving similar, non-switching related training (Karbach & Kray, 2009). In this study, demands were not only on task-set selection, but also on interference control and on goal maintenance, thus requiring use of multiple cognitive control mechanisms in one task. The fact that this intervention led to generalizable learning highlights the importance of engaging multiple mechanisms in training tasks.

Multitasking

Elderly adults generally experience greater dual-tasking costs compared to young, even when taking age-related general slowing into account (Bherer et al., 2005; Bherer et al., 2008; Verhaeghen et al., 2003). Evidence from a recent fMRI study implies that during dual-tasking, elderly are unable to sufficiently disengage from the interruption by the second task and therefore fail to switch back to the appropriate functional network, which causes greater difficulty with dual-tasking (Clapp et al., 2011). Intervention studies show that elderly are able to benefit from dual-task training at the same rate as young. Bherer et al. (2005) trained elderly on a three-week long paradigm where visual identification and auditory discrimination were performed either concurrently or separately. Response latency was reduced in elderly to the same extent as in young adults, and accuracy improvement was even more pronounced among seniors, especially in the concurrent tasks. Near transfer was found on within-modality and cross-modality dual-task costs, and was as large (or larger) in old as in young. Assessment one month later suggested retention of the training effect. A follow-up study using two concurrent visual tasks reported similar training benefits among seniors (Bherer et al., 2008). This implies that improvement of multitasking can occur regardless of whether training consisted of same- or different-modality tasks.

Training on dual-tasking paradigms has also been suggested to transfer considerably to daily-life performance. When elderly and young subjects were trained on a driving simulation, which included a visual attention task and a visuomotor tracking task, elderly decreased their error count and response latencies to a greater extent than young adults (Hahn et al., 2010). On that same note, after computerized training on tasks combining working memory, attention, and manual control, older adults showed significant improvement in simulated driving performance (Cassavaugh & Kramer, 2009), where performance improvements on dual task effects were predictive of later driving performance improvements. Li et al. (2010) demonstrated transfer of visual discrimination multitasking to single- and double support standing balance. Hence, multitasking interventions show generalization to activities that are directly relevant to elderly.

Updating

Updating, an essential aspect of working memory, refers to monitoring incoming information for its relevance and accordingly adapting the content of working memory storage, and has been linked to activation in frontopolar and dorsolateral prefrontal cortex (Salmon et al., 1996; Van der Linden et al., 1999). Elderly performing updating tasks invest greater effort than young adults (Fiore et al., 2012). In one updating task, in which participants updated memory by remembering the smallest item on a list, four age groups (young, young-old, old, and old-old) were compared (De Beni & Palladino, 2004). Performance on this task declined more with increasing age, and older participants suffered more difficulty to suppress intrusions.

Despite age-related deficits, training of this paradigm in elderly has demonstrated opportunities for transfer. Near transfer to block-span performance was found after a 12-week training intervention (Buschkuehl et al., 2008) which included three different updating paradigms. Successful training on updating tasks was also done by Dahlin et al. (2008) who trained older adults on letter-memory updating, which requires keeping a string of letters in working memory and recalling the last 4 letters upon ending of the task. Elderly displayed increased task performance, which was maintained up to 18 months post-training, and training-related activation in striatum compared to controls,

One type of test often used to assess updating is the n-back paradigm, in which participants respond when the current stimulus matches that of n trials back. N-back tasks have been tested in elderly before, indicating the ability of elderly subjects to perform this task, even with increased working-memory demand (Jaeggi et al., 2009; Van Gerven et al., 2008; Verhaeghen & Basak, 2005). In young adults, training on this paradigm with a dual (visual and auditory) component is implied to lead to far transfer to fluid intelligence (Jaeggi et al., 2008; but see Moody (2009) for a critical evaluation).

To our knowledge, few longitudinal n-back training studies have been conducted in elderly. In one study, young and older adults were trained on a demanding spatial 2-back task (Li et al., 2008) which included blocks of regular spatial updating and trials which additionally required mental rotation. In old and young adults equally, near transfer to a more demanding spatial 3-back task and numerical 2-back and 3-back tasks was found. This performance was largely maintained 3 months after posttest. A 3-back spatial task has also been included as part of an effective multimodal training battery (Schmiedek et al., 2010). These results suggest that the older population might benefit from training on n-back tasks as well, although this claim has been contested by Engle and colleagues (see e.g. Shipstead et al., 2010). Further testing of this paradigm, including the possibility of transfer to untrained domains, seems a promising avenue for further research.

Inhibition

Inhibition refers to the suppression of thoughts or actions, usually in favor of other thoughts or actions. Inhibition may be at play at various levels: preventing irrelevant sources of information from capturing attention, preventing irrelevant contents of information from entering working memory, pre-empting rash decisions, suppressing impulsive or undesirable actions, or overriding prepotent responses in favor of more appropriate ones. Inhibition at the levels of attention and working memory have been associated with the functionality of frontoparietal systems (Hasher & Zacks, 1988), whereas inhibition in relation to decision-making and action have been linked to the integrity of frontostriatal circuitry (Ridderinkhof et al., 2004). A variety of tasks and tests have been proposed to assess inhibitory efficiency in older adults, but many of these tasks (and associated age effects) suffer from problems with task purity, methodological confounds, and other measurement issues that are characteristic of many so-called frontal-lobe tests (Rabbitt et al., 2001). Nonetheless, there appears to be consensus that the ability to inhibit spatial responses is relatively preserved, whereas the ability to actively inhibit prepotent responses shows more robust age effects (Andrés et al., 2008; Nieuwenhuis et al., 2000) in the form of reduced inhibitory control over reflexive saccades in the antisaccade task (for review, see Eenshuistra et al., 2004) and a reduced ability to interrupt actions that have already been initiated in the stop task (Williams et al., 1999).

To our knowledge, although a number of brain training studies have included inhibitory tasks in one form or other, no studies have focused specifically and systematically on whether the effects of old age on inhibitory efficiency can be remedied by training. One study reported that inhibitory skills can be trained in children (Thorell et al., 2009). That such training is feasible at least in principle in adults was demonstrated in a recent study with young adults, whose Go/NoGo proficiency improved after only a single and brief training session (Manuel et al., 2010). Evidence ubiquitously suggests age-related increases in susceptibility to interference in the Stroop task. Training studies have examined the effects of Stroop-task training in elderly, reporting performance improvement but no transfer (Davidson et al., 2003; Dulaney & Rogers, 1994). Unfortunately, the task impurity that characterizes the Stroop task (involving perceptual interference and task maintenance demands in addition to response inhibition, presumably leaving little age-related variance left to be explained by the latter) renders this task less suitable for studying the effects of age and training on inhibitory control. Using relatively more pure measures of response inhibition, age trends in inhibitory efficiency were reported in the Simon task (Maylor et al., 2011). Whether and to what extent these measures may benefit from training remains to be explored. Likewise, we are not aware of brain training studies using antisaccade tasks. Our own work has shown that antisaccade performance in the elderly may be improved considerably by motivational factors (Harsay et al., 2010), suggesting that there may be substantial space for improvement using brain training.

Summary

In sum, from the studies reviewed above it becomes evident that continuous training on cognitive control-based paradigms may not only lead to enhanced performance on the trained task, but may on occasion also extend to other, untrained, domains. This holds true in particular for tasks that capitalize in one way or other on cognitive flexibility, especially apparent in task switching paradigms (Karbach & Kray, 2009). Ideally, therefore, tasks should call on flexibility. They should engage multiple mechanisms of cognitive control at the same time, e.g. keeping a number of items in memory, shifting attention between tasks, inhibiting irrelevant stimuli while responding to another, and updating the memory trace. Subjects are thereby forced to divide their attention over a number of multimodal stimuli, creating a general state of alertness and preparedness for upcoming events that is likely to be generalized to functioning on other, nonrelated tasks.

ADDITIONAL PERSPECTIVES

A number of modalities that appear especially relevant to cognitive aging might be effectively trainable in this population, although so far there has been little investigation into these perspectives. First of all, decision-making and learning from mistakes are affected in old age, and a number of ideas to aid in dealing with these deficits are recounted below. Second, novelty can be an important key to add to training benefit in two separate ways, which will be argued here. Finally, memory strategy training has been shown to be effective in the elderly population. Although no evidence of far transfer currently exists, suggestions are given for ways to test this more thoroughly.

Decision-making

One domain that is also affected by age is decision-making and decision-learning (Brown & Ridderinkhof, 2009; Mohr et al., 2010). Older adults have more difficulty with stimulus-reward learning, taking longer to reach a criterion and displaying impaired feedback learning (Schmitt-Eliassen et al., 2007). Older individuals are generally more proficient at avoidance-learning compared to incentive-learning; they exhibit a bias to choose to avoid negative outcomes rather than gaining positive outcomes, thought to result from age-related loss of dopamine (Frank & Kong, 2008). Studies assessing learning abilities in elderly using the Iowa Gambling Task, where one needs to learn to choose cards from the most beneficial deck to optimize reward, have resulted in mixed findings. Some suggest that elderly do not sufficiently learn to pick the most profitable deck (Fein et al., 2007); others find that this impaired learning only applies to a subgroup of elderly (Denburg et al., 2006), illustrating the individual variation in this population. Increased age has also been found to be related to greater reward-related risk-taking (Cavanagh et al., 2012), in particular when learning has led to risk-avoiding behavior (Mata et al., 2011). Furthermore, it seems that elderly display an alternate activation pattern of the ventral striatum during reward anticipation and delivery. Although in elderly the ventral striatum is engaged to represent reward value, this region often fails to show activation when anticipating reward (Schott et al., 2007). Unlike in young, there is a failure to activate the insula during loss prediction (Samanez-Larkin et al., 2007), demonstrating their ability to process reward value but an inability to engage the necessary regions during anticipation.

Delay discounting refers to the preference for more immediate, smaller rewards relative to later, larger rewards. The ability to forego an immediate reward in favor of some future interest (a crucial aspect of decision-making, also in a variety of daily-life decisions) has been associated with striatal dopamine; hence, one might expect the proficiency of delay discounting to decline with age. Results are mixed and contradictory, however (Chao et al., 2009; Jimura et al., 2011; Lockenhoff et al., 2011; Reimers et al., 2009), preventing us from drawing firm conclusions at this stage.

Given these patterns of aging-related deficits in decision-making and decision-learning, and the importance for independently functioning elderly to be able to make essential decisions for themselves, one might expect decision-learning to be included in one way or other in brain training programs. We are not aware, however, of any training studies in the realm of outcome optimization. Yet, the success of such training seems feasible. For instance, anticipation of a rewarding outcome has been shown to motivate successful optimization strategies in elderly (Denburg et al., 2006; Harsay et al., 2010). Along another avenue, older decision makers appear to base their decisions on less information than younger decision makers, since this leads to only small losses in decision quality (Mata & Nunes, 2010). Thus, brain training programs might focus on training the ability to select target information economically. Moreover, aging appears to be associated specifically with deficits in rule-based decision-making processes (Mata et al., 2011) suggesting that training protocols can be targeted to learning simple and (as learning progresses) more complex decision rules in choice games, and to learning that rule-based decisions lead to favorable outcomes more often than, for instance, similarity-based decisions.

Novelty

Cognitive processes can be more adequately stimulated by including the important ingredient of novelty: an item, task, or activity that is unfamiliar and has not yet become subject to automatization. There are two ways in which novelty inclusion can benefit training studies and lead to reduced cognitive decline: to improve performance on existing tasks by direct inclusion of novel stimuli within training tasks, and to improve performance on new tasks by creating novel experiences and activities as the core of training. Along these lines, besides inducing novelty within tasks, an enriched environment can offer a similar effect, challenging the neuronal system to develop or protecting it from negative aging influences, as has been shown in aging animals (Kempermann et al., 2002; Winocur, 1998) as well as humans (Karp et al., 2006).

One type of intervention may contribute to protracted cognitive decline by adding features of novelty to an existing task. Stimulus repetition often leads to a decrease in neural activity as a result of more efficient neural processing (Ranganath & Rainer, 2003); by contrast, inclusion of novel stimuli is often followed by an increase in activity, and has been demonstrated to enhance synaptic plasticity, thereby posing an advantage for interventions.

Neuromodulation is believed to play an important role in the encoding of novel information into memory. Acetylcholine as well as norepinephrine have been shown to facilitate consolidation of novel stimuli by increasing the firing rate and enhancing responses to stimuli. This is also illustrated by administration of anticholinergics, which attenuates electrophysiological and hemodynamic expression of the effects of novel compared to familiar stimuli (Ranganath & Rainer, 2003).

Düzel et al. (2010) argue that novelty processing in the brain can enhance plasticity by boosting dopamine to benefit learning and memory and allow long-term consolidation to take place within the hippocampus. Dopaminergic neuromodulation occurs during and after exposure to novel stimuli, facilitating long-term potentiation and leading to consolidated synaptic plasticity. The authors suggest an integrative model of exploratory drive and neuronal plasticity to explain the connections between dopamine, novelty and plasticity, specifically in old age. According to this model, an individual is motivated to perform exploratory behavior following novelty expectation. As dopaminergic neuromodulation is subject to deterioration with increased age, elderly generally receive less reinforcement from novelty and would naturally tend less towards seeking novel stimuli in their environments, thereby creating less opportunity for plasticity and learning to take place. Although older adults benefit less from inclusion of novelty compared to younger individuals, they are still thought to benefit from a boost of dopamine to create a better learning opportunity.

Few studies have examined the role of novelty in protracting neurocognitive decline directly. One line of studies used randomized trials to investigate training abilities in elderly participants by teaching and training skills in novel activities. For instance, Bugos et al. (2007) explored individual piano instruction as a cognitive intervention in the elderly population. A group of musically naïve elderly subjects were given weekly piano and music theory lessons and were required to practice independently for 3 hours each week for a period of 6 months. Compared to a control group who received no training, transfer of training was seen on Digit Symbol (a subtest of the WAIS) and the Trail Making Test, suggesting that music training led to improvement of concentration, attention, and planning abilities. Likewise, Boyke et al. (2008) studied a group of healthy elderly learning to juggle. They were given three months to learn and practice, and MRI scans were made directly before and after training, and three months after training had ended. Changes included grey-matter increases in brain areas responsible for processing of complex visual movement, and did not appear in the control group. These structural changes occurred even in individuals who were not able to perform satisfactorily at the time of testing, suggesting neuronal plasticity even among seniors who take longer to learn a new ability. A follow-up study using a small sample of young adults suggests that these structural changes might be produced by learning of the novel skill per se, with little further contribution from the amount of practice or the eventual quantitative increases in performance (Driemeyer et al., 2008). Unfortunately, the latter study did not make use of any control group, so that further investigation of how much practice is needed to produce structural changes remains necessary. However, so far it seems that learning novel activities can lead to improvement and transfer to other tasks, as well as to structural brain changes in old age.

Novel and challenging experiences during the lifetime are thought to also benefit cognition in old age. Neurocognitive aging processes may speed up when individuals no longer engage in work-related or social activities and hence withdraw from stimulating environments that frequently present novel stimuli or challenges (Aichberger et al., 2010; Roberts et al., 2011), possibly through weakening of neuronal connections (Cerella & Hale, 1994). Actively taking part in cognitively challenging activities is thought to function as a protective factor against cognitive decline and even decreases the risk of development of age-related diseases (Bialystok et al., 2007; Karp et al., 2006; Yaffe et al., 2009). There appears to be a strong connection between involvement in complex and challenging work during early adult life, and subsequent intellectual functioning in old age (Schooler et al., 1999). Job complexity is also believed to offer a protective factor against dementia (Potter et al., 2007). However, these studies were not able to control for confounds, leaving open the possibility that the mentioned relationship between complexity and novelty in early life and functioning in older age is bidirectional, that is, although a stimulating work environment probably affects workers' cognitive wellbeing and challenges them to broaden their intellectual horizons, individuals' already existing intellectual functioning also causes people to choose for more challenging and intellectual vocations to match their abilities. Bosma et al. (2003) analyzed the protective effects of work load on later cognitive functioning longitudinally, but controlled for a number of confounds including education and baseline intellectual abilities. When adjusting for these factors, individuals with higher workload showed a greatly decreased risk of developing later cognitive impairment.

These outcomes emphasize the promise held by the training of novel skills or the inclusion of novel stimuli in training programs. Novelty not only primes the neuronal system to prepare for learning, but the addition of continuous novel stimulation itself, be it in a standardized task or in learning a new ability, also helps build new connections and could add to individuals' motivation, providing important benefits for maintaining cognitive wellness.

Memory strategies

Several aspects of working memory training, such as updating, have been reviewed above. One could argue that these concentrate on training processes. This approach must be distinguished from developing new memory strategies (Kliegel & Bürki, 2012). These have a long history (Yates, 1966) and there is a considerable body of literature that demonstrates their effectiveness (Higbee, 2001). This suggests that they may also be applicable as a successful form of brain training in the elderly. Memory strategies are often taught as part of a more general memory training, which can range from learning a simple mnemonic strategy to extensive practice with a wide range of memory techniques. Rebok et al. (2007) reviewed almost 300 memory training studies with older adults using explicit criteria to judge whether the improvements due to a certain type of training could be considered evidence-based. According to the criteria, a type of training showed a beneficial effect if more than 50% of the outcome measures were both statistically significant between-group treatment effects (within-group studies were compared with baseline) and had effect sizes of at least 0.20. Evidence criteria for a certain type of memory training stipulated, furthermore, that there be at least two such studies with beneficial effects, with a minimum of 30 participants in total. Of the 218 studies considered by Rebok et al. (2007), 39 studies contribute support to 16 types of memory training which effects could be considered evidence-based. In particular, studies involving instruction in multiple mnemonic techniques led to lasting improvements (Ball et al., 2002; Dunlosky et al., 2003; Hill et al., 1990; Stigsdotter & Backman, 1989). Also, training specific strategies such as visual memory support (Sharps & Price-Sharps, 1996) the story mnemonic (Hill et al., 1991) and the classic loci method (Kliegl et al., 1989; Hill et al., 1991) gave significant results that qualified on the evidence-based criteria. Rebok et al. (2007, pg. 54) conclude that these findings suggest "…that there are potentially several evidence-based options for older adults who wish to improve their memory and reduce memory problems."

Whereas there are clear benefits from certain types of strategy-based memory training, it is not clear at this point whether they also give rise to long-term benefits. Zelinsky (2009) for example, concludes that training specific mnemonic strategies in isolation does not seem to lead to far transfer. Few studies have attempted extensive training on a variety of strategies. One example is a recent study by Craik et al. (2007) who instructed 49 older adults in a variety of mnemonic strategies (among other aspects of the training). The instruction sessions encouraged subjects to practice and find their own optimal combination, but there was no formal guidance, nor was there a computerized training that supported the optimization process. Craik et al. (2007) found no improvements on primary memory or working memory, but they did find a lasting improvement on episodic memory. A limitation of this study is that as part of the design, half the subjects had to wait three months after entering the study and initial orientation before they received the majority of the training. As the authors remark, this led a loss of motivation in the late group and hence to a loss of power in the experiment.

Craik et al. (2007) allowed subjects to control and combine their optimal strategies. Complete self-generation of strategies is thought to be a particularly effective method. In Lustig & Flegal (2008) subjects were shown individually presented words to encode and remember as well as possible. They were assigned to either a condition in which they learned to use a specific encoding strategy, or a condition in which they could choose their own strategy. Transfer to an unrelated task was found only in the strategy choice condition. This suggests that it is most beneficial to engage and train preserved albeit dormant functions in elderly by letting them initiate their own optimal strategy, in order for deep encoding processes to occur to lead to more generalizable results. Derwinger et al. (2005) also found that in older individuals, self-generation of strategies is most optimal. Although subjects using learned mnemonic strategies and self-generated strategies to memorize 4-digit numbers retained the same amount of information on the short term memory tasks, long-term recollection was better in the strategy-choice condition.

We find evidence for beneficial effects of strategy-based memory training, though successful studies that yield far transfer are currently lacking. We suggest the use of a computerized approach in order to ensure that strategies are indeed being trained and to help subjects in their development and application.

Summary

A number of additional modalities have been discussed that could potentially be used to add to effective training purposes, though more research is needed to confirm this. Given the aging-related deficits in decision-making and decision-learning, aspects of decision-learning might be included in training programs by focusing, for instance, on reward anticipation or rule-based decision-making. Novelty seems to be an important factor for more lasting effects of brain training, especially in elderly, and inclusion of novel stimuli or tasks could motivate elderly to invest more effort and energy into learning. In strategy-based memory training, most success is to be expected from studies that employ a variety of memory strategies, allowing considerable freedom to select optimal combinations of these, and include extensive practice.

THE INDIVIDUAL PICTURE

Variation within the aging population

One major caveat in much of the literature on brain training research concerns individual differences in the aging population. First, aging studies frequently use a comparison of retired, independent elderly of various different backgrounds to young adults, often psychology students. Besides the fact that both groups are often recruited from different sources, which impacts the validity of these studies, students and retirees are likely to differ in several other ways than age alone (e.g., length and type of education or exposure to technology), making it more difficult to attribute any observed differences directly to age-related decline and skewing the implications of age-related cognitive decline as derived from these results.

Second, and perhaps even more important, in the current literature elderly individuals are often measured as a group, without paying attention to the existing and evident differences between individuals. Elderly are likely to differ more from each other than young adults do. Genetic and environmental, traumatic and advantageous influences have a lifelong effect on each person's brain and behavior (Bialystok et al., 2004; Christensen et al., 1999; Lindenberger et al., 2008), thus exaggerating inter-individual variability as the individuals grow older. To draw conclusions on trainability of a certain task based on the mean performance of a group of elderly does little justice to individuals' strengths and weaknesses and paints a picture of the potential effects of training that is not sufficiently representative as it tends to blend all nuances in the color palette into a single shade of grey. Certain individuals might have a larger rate of cognitive decline than others, while yet others might show little decline at all. Variability in cognitive performance may result also from, for instance, illness or depression (Christensen et al., 1999). Such variation is likely to cause inconsistencies within training studies, resulting in poor conclusions about the success of certain interventions or inaccurate rejections of training paradigms that could be helpful to some, but might not work for most. Some studies that attempt to take individual variation in baseline parameters (such as working-memory capacity or general processing efficiency) into account even arrive at the conclusion that age-related differences in cognitive performance can be reduced to age-related differences in these baseline parameters (Della Sala et al., 2010; Eenshuistra et al., 2004). Current brain training research is based on the question whether a paradigm is either successful or unsuccessful; instead, we might profit more from asking for whom the training works, and how these individuals vary from the rest, in terms of behavioral and neuroimaging measures. Each person is likely to benefit from different training approaches (Yaffe et al., 2009). Some might benefit more from some tasks than from others, and some people might need more intensive training, whereas others lose motivation because training tasks do not pose enough of a challenge. Adaptive training is tailored to the needs and abilities of the individual, increasing difficulty levels as one gets better and decreasing them as more errors occur. Adding an adaptive component to the training is therefore crucial to allow people to train at their own level and keep each person challenged and motivated. Most training studies do not pay attention to this aspect, though some have (Ball et al., 2007; Mahncke et al., 2006; Smith et al., 2009). Lustig and Flegal (2008) showed that memory training performance was most effective when subjects were allowed to explore and initiate their own latent optimal strategy. It seems crucial that, during training, subjects should experience success yet stay challenged enough to increase performance. Finally, the gains associated with working-memory training were found to depend on genotypes related to the expression of dopamine in the substantia nigra (Bellander et al., 2011).

For those individuals who benefit less from brain training, alternative intervention possibilities can be explored. An important challenge, then, lies in identifying predictors of individual differences in trainability. These predictors could consist of certain neurocognitive test results, but importantly also of data on individual neural hard-wiring: neuromodulation, regional brain volume, structural and functional connectivity, or functional activation patterns. In the next section we assess in more detail the benefits that covariance-based neuroimaging techniques might provide in helping us understand individual differences in cognitive decline and trainability.

Imaging individual differences

Recent progress has advanced our insight in functional and structural alterations in healthy aging as related to individual performance differences (independent of baseline structural volume or age per se). For instance, BOLD (de)activation patterns can illustrate associations with reduced or retained performance. Two groups of elderly who had shown similar IQ at age 11 but whose IQ scores diverged at age 70 were compared, thus forming a group of cognitive “sustainers” and “decliners” (Waiter et al., 2008). fMRI data of the elderly group was subsequently compared to that of a young subject group. Whereas neural activation for the sustainer group did not vary from the brain regions active in young during a visual inspection task, decliners showed deactivation in a number of these areas; neural activation was found to predict individual preservation of complex reasoning skills. Similarly, in the memory domain, increased neural activation during an emotional word judgment task was observed in young adults and in a subgroup of elderly with normal performance, but not in elderly with declined memory performance (Daselaar et al., 2003). Variance in episodic recall performance has also been linked to hippocampal volume and activation change (Persson et al., 2005).

Evidence that fMRI results could be applied to predict clinical cognitive decline comes from O'Brien et al. (2010) demonstrating that individuals without signs of dementia at baseline but with a Clinical Dementia Rating (CDR) score of 0.5 showed a decline in hippocampal activity on an associative memory task over a period of 2 years, whereas activation patterns of those with a CDR score of 0 remained the same.

At the structural level, more complex sulcal folding was correlated with higher maintenance of cognitive processing speed (Kochunov et al., 2010; Liu et al., 2011). Measurement of postsynaptic markers has also been related to cognitive performance in elderly. Using PET, increased caudate dopamine uptake was found to be related to higher working memory capacity while dopamine uptake in putamen was connected to increased motor speed (Landau et al., 2009). D2 receptor binding has been found to account for differences in individual cognitive performance more than age did (Bäckman et al., 2000), especially in motor functions and tasks dependent on frontal brain areas (Volkow et al., 1998). These and more recent findings suggest that individual age-related changes in prefrontal and striatal dopaminergic systems underlie performance decline (e.g. Bennett et al., 2011; Klostermann et al., 2012; Samanez-Larkin et al., 2011).

In future studies, combining some of these imaging techniques to examine the individual differences in trainability among elderly could lead to important insights about which individuals do or do not benefit from specific types of training, so that alternative interventions can be considered. For instance, striatal volume pretraining was found to account for improvement of young adults on a strategy video game (Erickson et al., 2010). Nucleus accumbens volume predicted success during early training while larger dorsal striatum volume was associated with improvement of performance throughout the training. To our knowledge, similar neuroimaging perspectives examining predictors of individual training success have currently not been investigated in the elderly brain training literature. In one study (Engvig et al., 2012) elderly subjects were scanned before and after memory training using DTI to measure changes in white matter tracts, and found an increase in fractional anisotropy (FA) in the training group, demonstrating the sensitivity of DTI to display differences in white matter over a period of 10 weeks. Moreover, individual memory improvement was significantly related to strength of FA change. This illustrates the possibility to show individual differences in training success in elderly, allowing future research to explore the potential of this methodology.

CONCLUSION

In pursuit of successful cognitive interventions, different training activities have been used to preserve and improve cognitive functioning in the aging population. Despite ample evidence showing that improvement is indeed possible, results are not consistently positive. We have sketched a number of ways in which future interventions could promote robust and generalized preservation of function. In order to attain long-term retention and transfer, plasticity is key. Cognitive processes can be more adequately stimulated by including the important ingredient of variability: requiring subjects to integrate cognitive functions rather than training separate mechanisms. Because cognitive domains are behaviorally and neurologically intertwined, maximal profit is reached if not just one, but multiple functions are engaged with the tasks at hand. We therefore suggest that brain training tasks be multimodal, tax cognitive flexibility, and capitalize on novelty to stimulate plasticity to the highest extent. These properties tend not to be naturally included in most older adults' daily activities. Yet, this very fact points out the relevance of using these properties in this population in order to offer an optimally challenging environment. A successful brain training program should preferably include a range of different tasks to engage a multitude of functions, as well as continually offer something new in order for the neuronal system to remain challenged and to create possibilities of maximum enhancement in this population. We further argue for the importance of paying attention to individual differences in training benefit. This is possible both by incorporating adaptive elements into training, thus allowing each individual to improve at their own pace, according to their already existing abilities and in tune with their individual and momentary motivational needs. Finally, we recommend the application of innovative covariance-based neuroimaging methods to studies of brain training to investigate neural predictors of individual differences in trainability.

Chapter 3

Cognitive flexibility training: A large-scale multimodal adaptive active-control intervention study in healthy older adults.

Based on:

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ABSTRACT

As aging is associated with cognitive decline, particularly in the executive functions, it is essential to effectively improve cognition in older adults. Online cognitive training is currently a popular, though controversial method. Although some changes seem possible in older adults through training, far transfer and longitudinal maintenance are rarely seen. Based on previous literature we created a unique, state-of-the-art intervention study by incorporating frequent sessions and flexible, novel, adaptive training tasks, along with an active control group. We created a program called TAPASS (Training Project Amsterdam Seniors and Stroke), a randomized controlled trial. Healthy older adults (60-80 years) were assigned to a frequent- or infrequent switching experimental condition or to the active control group and performed 58 half-hour sessions over the course of 12 weeks. Effects on executive functioning, processing- and psychomotor speed, planning, verbal long term memory, verbal fluency, and reasoning were measured on four time points before, during and after the training. Additionally, we examined the explorative question which individual aspects added to training benefit. Besides improvements on the training, we found significant time effects on multiple transfer tasks in all three groups that likely reflected retest effects. No training-specific improvements were detected, and we did not find evidence of additional benefits of individual characteristics. Judging from these results, the therapeutic value of using commercially available training games to train the aging brain is modest, though any apparent effects should be ascribed more to expectancy and motivation than to the elements in our training protocol. Our results emphasize the importance of using parallel tests as outcome measures for transfer and including both active and passive control conditions. Further investigation into different training methods is advised, including stimulating social interaction and the use of more variable, novel, group-based yet individual-adjusted exercises.

INTRODUCTION

We live in a time of great societal changes in the Western world. Due in part to dramatic improvements in medical science, our aging population is expanding rapidly. As aging is associated with decreased cognitive functioning, the prevalence of age-related cognitive decline is an increasingly important issue. Decline of cognitive control, memory, and decision-making, among other functions, leads to greater dependence on family members and society. With recent increments of the retirement age in many countries, increasing numbers of older workers are expected to contribute to the workforce, but may cognitively fall behind. In order to ensure that older adults can live and work independently for as long as possible, research into possibilities of reducing this age-related decline of functioning is a pressing matter.

Enhancing cognitive functions or limiting their decline using cognitive training is currently a popular topic. Effectiveness of such trainings has been investigated with numerous intervention studies, for instance working memory training (Buschkuehl et al., 2008; Richmond et al., 2011; Rose et al., 2015), virtual reality training (Optale et al., 2010; Lövdén et al., 2012), and game training (Basak et al., 2008; Nouchi et al., 2012; van Muijden et al., 2012; Baniqued et al., 2013; Toril et al., 2016). Benefits of using at-home computer-based training programs are evident: they require no face-to-face contact, are easy to administer, and do not require traveling, which is especially advantageous when catering to more physically impaired individuals. Furthermore, they are cost efficient, and can be customized to a personal level in order to keep motivation optimal. In addition to the possible benefits for cognition, young and older adults also enjoy playing computer games in order to challenge themselves and for reasons of entertainment and—for certain games—social rewards (Allaire et al., 2013; Whitbourne et al., 2013). The gaming industry has conveniently caught on to this trend. As a result, countless commercial training websites and stand-alone applications offer a whole range of games that promise to contribute to cognitive reserve and slowed decline. Research indicates, however, that not all types of games are enjoyed equally by the older population. Realistic first-person shooter games, though cognitively challenging, are perceived negatively by many older adults (Nap et al., 2009; McKay & Maki, 2010). Generally, casual games or games comprised of short mathematical- or memory activities are rated as most enjoyable and lead to higher compliance and beliefs about enhancement (Nap et al., 2009; Boot et al., 2013).

Despite its popularity and market potential, the effectiveness of brain training remains a controversial topic. Results are inconsistent (Au et al., 2015; Dougherty et al., 2016) with some producing no transfer effects at all (Ackerman et al., 2010; Lee et al., 2012). Near transfer is often reported, especially after multitasking or task-switching designs (Karbach & Kray, 2009; Wang et al., 2011; Anguera et al., 2013) though far transfer is scarcely found (Green & Bavelier, 2008; Park & Bischof, 2013). Furthermore, a large variability in the degree of individual response to cognitive training is often observed (Langbaum et al., 2009; Melby-Lervåg et al., 2016). For instance, general training benefit is often found to be dependent on higher age and lower baseline cognitive abilities, and in some cases on training gain and education (Verhaeghen et al., 1992; Bissig & Lustig, 2007; Langbaum et al., 2009; Zinke et al., 2014) although there is some evidence of increasing benefit after lower baseline scores (Ball et al., 2007; Whitlock et al., 2012).

Previous research suggests that stimulating alternating cognitive processes in subjects fosters transfer to untrained behavioral measures (Bherer et al., 2008; Karbach & Kray, 2009; Buitenweg et al., 2012). The ability to adjust one's responses to the demand of a new situation, known as cognitive flexibility (Buitenweg et al., 2012), is a core executive function, facilitating the functioning of higher order functions (Berry et al., 2016; Buttelmann & Karbach, 2017). That being the case, cognitive flexibility proves essential for both cognitive and everyday functioning (Logue & Gould, 2014) and has been seen to be ameliorated by aerobic exercise (Masley et al., 2009), positive mood (Hirt et al., 2008), and video game play (Colzato et al., 2010; Glass et al., 2013). For this reason, it is of importance to investigate whether capitalizing on cognitive flexibility within a training would result in stronger intervention effects than without this element.

We and others (e.g. Buitenweg et al., 2012; Slagter, 2012; van de Ven et al., 2016) raised a number of problematic issues often encountered in the training research literature. Among them were brief training periods (limited numbers of session/days/weeks), small sample sizes, absence of active control conditions, inapt competitive motivational incentives, and use of unimodal training tasks (incurring task-specific and even stimulus-specific rather than process-specific training benefits). On the basis of our review of optimal study design, training efficacy, and neurocognitive profiles of successful aging (Buitenweg et al., 2012), we suggested adding the elements of flexibility, novelty (Noice & Noice,

2008) and adaptiveness (Kelly et al., 2014) to training protocols to increase the chances of finding positive effects on cognitive functioning.

Due to the encountered issues in the literature, the current situation in the training field is inconclusive on training generalizability. We therefore created a unique, state-of-the-art, 12-week intervention study incorporating multimodal, novel, adaptive training games and frequent sessions. To induce flexibility, we transformed the idea of task switching training, which has led to far transfer in Karbach & Kray (2009). We integrated switching between training games to create a more ecologically valid intervention, while using a number of switching tasks as our transfer measures. Besides this, we employed a number of measures with alternate (parallel) forms in order to minimize retest effects. In addition to including a number of essential elements, we are the first study adding flexibility as a key ingredient to training. We were especially interested in the question whether shifting attention between multiple functions during the training would transfer to decreasing switch costs. For this purpose, we required a task in which to present both alternating and repeating cues, which was possible using the switching paradigm previously used by Rogers & Monsell (1995). However, to evaluate effects on the entire construct of task switching, we combined additional measures in our secondary analysis. We included the clinically validated Delis-Kaplan Executive Function System – Trail Making Test and the online version of this task, in which (unlike in our main switch task) every response requires a switch, but participants still access basic knowledge of number- and letter systems. To incorporate a more ecologically valid measure of task switching, we also added the switch condition of the semantic fluency test, in which switching between activations of more covert representations is required.

We investigated whether an online training incorporating these crucial components can lead to transfer in an elderly population. Our training program consisted of two experimental conditions and an active control condition in a program called TAPASS (Training Project Amsterdam Seniors and Stroke). The TAPASS program has been used to determine the effects of cognitive flexibility training in stroke survivors by adding to the usual rehabilitation care (van de Ven et al., 2015). Here, we focus on effectiveness of this program in the healthy aging population. Experimental groups differed in flexibility, novelty and adaptiveness. Higher flexibility was created by having the subject switch more often in a session between cognitive domains from game to game. High novelty implied exposure to more different cognitive domains within one session. Adaptiveness refers to the extent to which game difficulty can be adapted dynamically to an individual's performance. The frequent switching (FS) group scored high on flexibility, novelty and adaptiveness. The infrequent switching (IS) group contained high novelty and adaptiveness but low flexibility, and the mock training (MT) scored low on all three features. We investigated whether there are benefits of the experimental training on cognitive functioning, and if so, whether the switching component adds extra value to these effects. In addition, we explored the question whether training efficacy is modulated by individual characteristics, such as age, baseline functioning, or education.

As the current intervention is especially focused on inducing flexibility, we expected transfer to occur in functions of executive control (Buchler et al., 2008; Karbach & Kray, 2009; Buitenweg et al., 2012). Based on a classification model by Miyake et al., 2000) these are often separated into updating, inhibition, and shifting (dual tasking and task switching). Therefore, our main analysis was centered around measures of these constructs. For reasons of equal comparison, for the primary analysis we selected tasks that were all administered by computer at the lab. In our secondary analysis, we included additional assessments of working memory and task switching as well as tasks from other domains. Due to their dependence on the frontal lobe, planning and verbal fluency are often counted among the executive functions as well (Fisk & Sharp, 2004; Phillips et al., 2006; Lewis & Miller, 2007) and can be subject to decline in older adults (Auriacombe et al., 2001; Sullivan et al., 2009; Kim et al., 2013). For this reason, we chose to include measures within these domains. In addition to the executive functions, processing speed often declines in later life (Salthouse, 2000), though training with a similar intervention has been seen to lead to improvements in this domain (Nouchi et al., 2012). As most of our training tasks included fast paced, timed games, we were interested to see whether the training would generalize to measures of processing speed. Additionally, as using the computer mouse was an important part in this study in completing the training tasks as well as the transfer measures, we also decided to include tasks of psychomotor speed. Finally, two more functions often found to diminish in older adults are reasoning ability and verbal long term memory (Davis et al., 2003; Harada et al., 2013), which have also seen improvements after similar interventions (Au et al., 2015; Barban et al., 2015). Measures of these constructs have been added to our battery of transfer tasks.

The purpose of this study was to test the hypothesis that a 12-week cognitive flexibility training would improve cognitive functions in healthy older adults. We expected to see the largest transfer effects on executive control performance after the frequent switch training, smaller effects after the infrequent switch training, and little to no effects after the mock training. We expected differences between conditions to be smaller, yet in the same direction, on performance of other domains.

METHODS

Participants

Our study entailed a randomized controlled double-blind design. Participants were recruited via media campaigns (pitch talks on regional radio stations and articles in local newspapers) and from a database of healthy older adults interested in participation in psychological research (*www.seniorlab.nl*). A total of 249 healthy participants signed up online on *www.tapass.nl* and were assessed for eligibility. Inclusion criteria included age above 60, willingness and cognitive ability to finish the 12-week training program, and daily access to a computer with internet connection. Exclusion criteria were a history of neuropsychiatric disorders, TIA or stroke, strongly impairing visual deficits, and colorblindness. Additionally, mental condition was estimated with the Telephone Interview Cognitive Status (TICS; Brandt et al., 1988): individuals scoring below 26 on this test were excluded. Eleven individuals did not fit the inclusion criteria and were excluded. Twenty-nine individuals withdrew before randomization, and another 51 before the first test session, due to health- and technical issues, or lack of time. The remaining 158 subjects were included in the final sample. Subjects were randomly assigned to one of three conditions, with the exception of partners/spouses, who were always assigned to the same group. We minimized asymmetry in our three conditions using a minimization program (Minimpy; Saghaei & Saghaei, 2011) over the factors age, computer experience, TICS score, gender, and education. The minimization procedure was carried out by the principal investigators only. All subjects were given the same information regarding the intention of the experiment. They were told they would be placed in one of three different conditions, without explicit mention of a control condition. A schematic overview of the study design can be found in Figure 1.

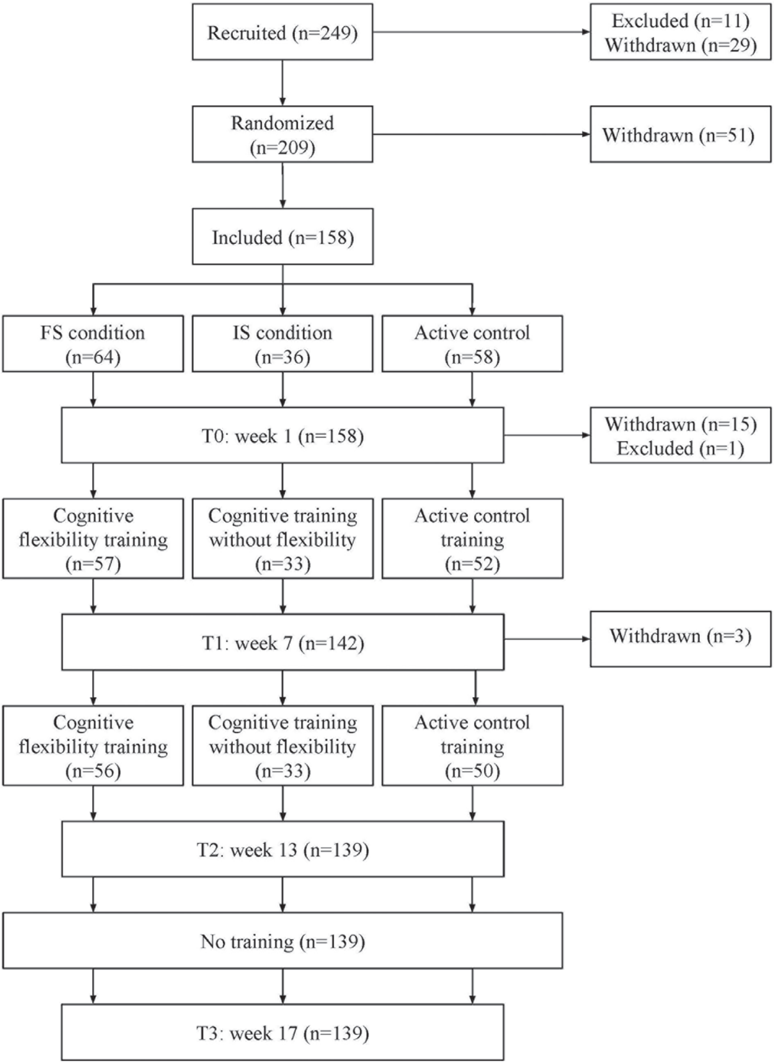


Figure 1. Flow chartof the study design. FS= frequent switching; IS= infrequent switching

Participants were compensated for travel costs and received free unlimited access to all games on *www.braingymmer.com*. Full written informed consent was given by all subjects prior to participation. The study was approved by the local Ethics Committee of the University of Amsterdam and registered under number 2012-BC-2566. All procedures were conducted in compliance with the Declaration of Helsinki, relevant laws, and institutional guidelines.

Study Protocol

A battery of online tests (Neurotask BV, 2012) was devised to measure effects of the training at 4 points in time: at baseline (T0), after 6 weeks of training (T1), after 12 weeks of training (T2) and 4 weeks post-training (T3). On T0 and T2, subjects also visited the university for a series of neuropsychological tests and computer tasks, and a small set of cognitive tests was administered via a link in the email. Additionally, subjective effects were measured using a series of questionnaires at all time points, and a subgroup of participants underwent Magnetic Resonance Imaging (MRI) scanning at T0 and T2. Results of these subjective and MRI measures will be reported separately. Testing on T0 and T2 was spread out over 3 different days, and on T1 and T3 over 2 days. Both the order of the test days for T0 and T2 and order of testing within the neuropsychological test battery were counterbalanced between subjects.

Neuropsychological assessments were conducted by a trained junior psychologist, who was blind to the training condition. As a check, neuropsychological assessors were asked to guess the condition of the subject. A separate test assessor administered four computer tasks, and introduced the training to subjects using instruction videos and a demonstration of the training platform and games. After their first visit to the university, subjects received a personalized instruction booklet with illustrations reminding them how to log on to the testing and training platforms, how to play each game, and how to report technical problems. It also gave useful information beyond the training, for example, how to download a new browser, and the importance of good posture during computer use. Subjects were assigned to a member of the research team who called them weekly to biweekly with standardized questions, would offer motivation and feedback and who could solve (technical) problems. Subjects were encouraged to email or call their contact with more urgent problems.

Subjects were requested to train 5 times a week for a half hour, on days and times of their choosing. Training activity was monitored. If no login was encountered for 2 days, an automatic email was sent to the subject. Subjects were encouraged to finish the training in 12 consecutive weeks. If training had to be interrupted for a period of more than 2 days, such as during a holiday, the missed trainings were added to the end of the 12 weeks. After T3, participants filled out an exit questionnaire in which they were asked to rate the training and their own motivation. To verify blindness, we asked subjects to guess in which condition they had been included, in the case that one condition was less effective than the other. Subsequently, all subjects received login information for a lifetime account on the training website.

Intervention

All three training programs were based on the brain training website *www.braingymmer.com*. Games were originally programmed for the general population, but after running a pilot study, we altered the ones selected for our programs to fit the need of older participants. For example, many games commenced at too high speed and difficulty levels. This was adjusted in the research-dedicated ‘dashboard’ version of the platform. In this platform, game presentation order was fully preprogrammed in order to prevent individuals from selecting their own tasks. Subjects had some extra time to finish after the time-period set aside for playing a certain game had been reached (e.g., 3 minutes or 10 minutes) to prevent too abruptly ending a game.

All groups received the same amount and type of feedback after finishing a game or training session (see Supplementary Material 3.1). Additionally, all participants received standardized weekly to bi-weekly feedback and support from research team members who supervised them from baseline until 4 weeks post-training.

Cognitive training

We designed a cognitive training based on nine games in three domains: reasoning, working memory, and attention (see Supplementary Material 3.2). In designing our intervention, we chose not to include training games which too closely resembled any of our transfer tasks. Each game consisted of 20 levels, increasing in difficulty. The order of games was selected in such a way that two games following one another were never from the same domain, to optimize variability and flexibility.

Subject performance was rated with up to three stars at the end of each game block. Adaptiveness was implemented by asking subjects to continue to the next difficulty level when reaching two or three stars. In case a subject reached the highest level (20), he or she was asked to improve performance on previous levels with two stars.

Within the cognitive training we created two groups: frequent switching (FS) and infrequent switching (IS). In the FS group, one training session consisted of 10 games of three minutes each, thus requiring subjects to frequently switch to a task aimed to train a different cognitive function than the one before. In the IS group, three games of 10 minutes each were played so that switching between game domains occurred less frequently. In the first week only, in order for subjects to become familiar with the games, both groups played the games for 10 minutes each. By the end of the intervention, the time spent on each game was similar across participants in the FS and IS groups.

Mock training

For the mock training (MT), we selected games that provided equal visual stimulation and feedback and put equal demands on computer ability, but that were reduced in variability, flexibility, and adaptiveness, compared with the experimental conditions (see Supplementary Material 3). We selected four games that all put minimal demands on executive functions. Per session, subjects played three games of 10 minutes each, thus minimizing the need for flexibility. Unlike the FS and IS conditions, the MT was not adaptive. Although higher levels could be unlocked in the same manner, participants in the MT were instructed to remain on the same level for a week before continuing to the next level, regardless of the number of stars they received on a game.

Assessment tasks

The effects of the flexibility training were estimated using pre- and post-measures on an extensive battery of computer tasks, neuropsychological paper-and-pen tests and computerized versions of these tests. For detailed task descriptions, see van de Ven et al. (2015).

Principal analysis

For the principal analysis we used the executive functions as distinguished by Miyake et al. (2000): shifting (task switching and dual tasking), updating, and response inhibition. These were assessed with four computerized tasks.

Task switching and dual tasking performances were measured using modified versions of a commonly used switch task (Rogers & Monsell, 1995) and dual task (Stablum et al., 2007). The two tasks were combined to save time. Switch cost was calculated as the difference between reaction time on switch trials and no-switch trials in milliseconds, with higher switch cost signifying lower cognitive flexibility (Rogers & Monsell, 1995). Dual task performance was assessed by the reaction time on speeded responses of the dual trials (Stablum et al., 2007). Updating performance was measured using the N-back task as used by de Vries & Geurts (2014) including 0-back, 1-back and 2-back blocks. Performance on this task was calculated by the difference between the percentage correct on 2-back and percentage correct on 0-back items (Kirchner, 1958). The stop-signal task (Logan et al., 1984) was used to measure inhibition. Stop-signal reaction time (SSRT) was calculated by sorting all correct Go-trial reaction times, taking the time corresponding to the percentage of correct stop trials, and subtracting the mean stop-signal delay (SSD) from this number (Logan et al., 1984).

Secondary analysis

Effectiveness of the training on a larger scale was assessed by using neuropsychological tests from eight cognitive domains: task switching, psychomotor speed, processing speed, planning, reasoning, working memory, long term memory, and verbal fluency. In most domains we included multiple tests. For the RAVLT, letter fluency, category fluency with- and without switch condition, and Raven Progressive Matrices, we used alternate assessment forms. Where necessary, raw scores were recoded such that higher scores always represent better performance.

In the domain of task switching, we included the Delis-Kaplan Executive Function System – Trail Making Test (D-KEFS TMT; Condition 4), the Trail Making Test-B (TMT-B), and a separate switch condition of the semantic fluency task. The D-KEFS TMT concerned the number-letter switching subtask, with the performance score calculated as the total time in seconds to complete connecting letters and numbers in alternating order (i.e., 1, A, 2, B, etc.; Delis et al., 2001). The TMT-B pertained to the online version of this task, with performance assessed by the total time in seconds to complete connecting letters and numbers in alternating order (NeuroTask BV). The switch condition of the semantic fluency task consisted of alternating listing as many words as possible from two separate categories (male names and supermarket items, or female names and cities, counterbalanced over participants) in one minute. Outcome measure is the number of correct words in the switch condition, subtracted from the average number of correct words produced in the same categories without switching (Troyer et al., 1997).

For psychomotor speed, we used five tasks, four of which were assessed online. In the drag-and-drop task, participants were required to use their computer mouse to drag round or square shapes into an empty border. Outcome measure is the total time in milliseconds to complete the task (Neurotask BV). In the drag-to-grid task, participants dragged 25 squares into a 5x5 grid using the mouse. Performance was assessed by the total time in milliseconds to complete the task (Neurotask BV). The click task required participants to click a spiral of circles of decreasing sizes using the mouse, with total time in milliseconds to complete the task signifying the outcome measure (Neurotask BV). The D-KEFS TMT (Condition 5) concerned the motor speed condition, with the performance score calculated as the total time in seconds to complete tracing a dotted line between a number of circles (Delis et al., 2001). The TMT-A pertained to the online version of this task, with performance assessed by the total time in seconds to complete connecting numbers (NeuroTask BV).

Processing speed was measured using the Digit Symbol Coding test (Wechsler, 2000) and an online version of this task (Neurotask BV). In this task, participants are required to pair a series of numbers to the correct symbol according to a given rule. Outcome measure on this task is the correct number of items completed in 2 minutes.

In planning, we used the Tower of London (ToL). This concerned the online version (Neurotask BV) based on the original task by Culbertson & Zillmer (2005), in which participants move coloured beads from a starting position into the required position using a minimum amount of possible steps. Performance was assessed by the sum of the number of additional moves to solve the ToL, using a maximum score of 20.

In the reasoning domain, we included Raven's Progressive Matrices (Raven & Raven, 1998) as well as the Shipley Institute of living scale-2 (Zachary, 1991). For both reasoning tasks, the outcome measure we used was the total number correct on 20 items.

Working memory was assessed using 2 online tasks and 3 face-to-face tasks. A modified version of the Corsi block tapping task (Milner, 1971) was constructed for online assessment. Outcome measure was the longest correctly reproduced array of blocks (Neurotask BV). In the Paced Auditory Serial Addition Task (PASAT), participants needed to update the addition of numbers presented auditively. We administered two versions, in which numbers were delivered at a rate of respectively 3.4 seconds and 2.8 seconds. As an outcome measure, we calculated the mean percentage correct of both versions (Gronwall, 1977). The Operation Span consisted of a series of letters presented sequentially that needed to be remembered while solving mathematical equations (Unsworth et al., 2005). Outcome measure for the Operation Span was the total number of correctly remembered letters. In Rey's Auditory Verbal Learning Test (RAVLT)–direct, participants were presented with a series of words auditively for 5 trials and recalled as many words as possible after each trial. We used the total number of words remembered after 5 trials as an outcome measure (Saan & Deelman, 1986). Lastly, in Letter Number Sequencing (LNS), participants were required to recall a series of numbers and letters in increasing or alphabetical order (Wechsler, 2000). For this measure, we used the total number of correct items.

In verbal long term memory, the delayed item of the RAVLT was used, in which the outcome measure was the total number of words recalled after a delay of 20 minutes (Saan & Deelman, 1986).

In the domain of verbal fluency, we used a semantic fluency task and a letter fluency task. In the semantic fluency task, participants produced as many words as possible in two different categories (male names and supermarket items, or female names and cities, counterbalanced over participants), each in one minute (Thurstone, 1938). In the letter fluency task, participants produced as many words as possible starting with one of three different letters (P, G and R on one time point, K, O, and M on the other time point, counterbalanced over participants), each in one minute (Benton, Hamsher, & Sivan, 1989). For both tests, the outcome measure was the mean number of correct words.

To control for possible differences in fatigue and depression, we also examined baseline scores of the Checklist Individual Strength - Fatigue subscale (CIS-F) and the Hospital Anxiety Depression Scale - Depression subscale (HADS-D). The HADS-D (Zigmond & Snaith, 1983) measures subjective severity of depression and includes 7 items on a 4-point scale, with a maximum score of 21. The CIS-F (Vercoulen et al., 1997) measures subjective fatigue and the behavioral characteristics related to this concept. The scale consists of 8 items, with scores ranging from 8 to 56. A score of 35 is regularly used as a cut-off to denote severe fatigue (Worm-Smeitink et al., 2017).

We designed an exit scale with four separate questions assessing perceived difficulty and enjoyment of the games, self-rated general cognitive enhancement, and whether participants would continue using the training. Although the scale is not validated, it serves as a necessary tool to judge participants' present and future view of the training. Participants rated these questions on T2 and T3, on a 5-point Likert scale.

Training performance

Training performance in all three groups was measured using a mean training z-score as well as a mean gain score between T0 and T2. Level high scores were calculated as a percentage of the maximal score on that level. Next, all were added up to a total game score for each training game. For the experimental conditions, domain scores were also made by averaging the three total scores within each domain, and a final score by averaging all three domain scores. For the mock training, a final score was calculated by averaging over the four games. Subsequently, we computed a mean training score for all three training groups separately and transformed these to Z-scores to be able to compare mock training and experimental training groups relative to each other. The gain score was calculated by subtracting the mean score attained after the first 10 minutes of playing from the mean score attained at the end of training.

Statistical analysis

A first set of repeated-measures ANOVAs focused on the executive functions in the principal analysis, using time points T0 (baseline) and T2 (post-training). Scores on task switching and dual tasking, updating, and inhibition were used as dependent variables, with group (FS, IS or MT) as the independent variable. A second set of repeated-measures ANOVAs was carried out for the secondary measures. PASAT, ToL, TMT-A and TMT-B were transformed due to non-normality. PASAT scores were raised to the 3rd power, a square root transformation was used on ToL data, and TMT-A and TMT-B scores were transformed using the formula $1/x^{0.14}$. When necessary, outcome measures were rescored so that a positive value indicated improvement. We computed correlations between significant transfer tasks and age, TICS score, and workouts completed to determine whether to add them as covariates to the primary and secondary ANOVAs. Education level required nonparametric correlation analysis (Spearman’s Rho); all other measures used Pearson’s correlation coefficient. To explore the extent to which individual characteristics influenced training benefits, significantly correlated covariates were added to a repeated-measures ANCOVA of the primary and secondary measures. When a significant improvement was detected at T2 on one of the dependent variables also measured at T1 (after 6 weeks of training) and T3 (post-training follow up after 4 weeks), these were additionally added to the model to establish whether training effects were visible after 6 weeks of training, and whether they remained after training had ceased.

Grubbs’ Extreme Studentized Deviation test was used to detect outliers (Grubbs, 1950). We ran analyses with- and without outliers. All reported results are without outliers, unless otherwise specified. IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA) was used for all statistical analyses. Normality was checked using Shapiro-Wilk’s test and by evaluating skewness and kurtosis. A p-value of .05 (two-tailed if not mentioned otherwise) was considered significant. For all analyses, Bonferroni corrections for multiple testing were used. Greenhouse-Geisser corrected degrees of freedom were used whenever sphericity was violated, though for the purpose of legibility the original degrees of freedom are reported.

RESULTS

Of the 158 subjects we tested on baseline, 1 person was excluded before starting the training due to difficulty understanding the transfer tasks, 5 experienced substantial health problems, 3 reported lack of time, 5 did not enjoy the training, and another 5 experienced technical issues. There was no difference in gender, TICS score, education level, or training group between the final sample and dropouts (all p’s >.19) though there was a significant difference in age (sustainers M= 67.77, SD 5.0; dropouts M=72.3, SD=7.8, $t[20,134]$ = -2,454, p = 0.023). The subsequent results are based on the remaining 139 subjects (age 60–80, $M = 67.8$, 60.4% female, mean years of education 13.7).

Because participants receiving MRI scans were only assigned to either the frequent switch training or the mock training, these groups contain a higher number of participants than the infrequent switch condition. Fifty-six subjects were allocated to the frequent switch training, 33 subjects to the infrequent switch training, and 50 subjects to the mock training. Before training, the three training groups did not differ in gender, level of education, TICS score, age, or computer experience (all *p'*s >.26), as expected after minimization (see Table 1). There was also no difference in fatigue or depression (all p's >.48). Of the 14 participants whose fatigue scores exceeded the cut-off of 35, 5 were in the frequent switch condition, 5 in the active control and 4 in the infrequent switch condition. On the exit questionnaire, an equal number of people in each group reported having started new activities or training other than ours (χ^2(2, N=139)= .561, *p*=.77).

Table 1

Subject Demographics

	FS (n=56)	IS (n=33)	MT (n=50)	*p*
Age	67,8 ± 5,0	67,9 ± 5,4	67,6 ± 5,1	.97
Gender (% female)	64,3	63,6	54	.51
Level of education	5,9 ± 0,9	5,8 ± 0,7	5,9 ± 0,9	.76
TICS Score	35,6 ± 2,5	35,7 ± 2,3	35,2 ± 1,8	.51[a]
Prior computer use	5,6 ± 0,8	5,4 ± 1,6	5,8 ± 0,8	.11
CIS-F	20,0 ± 11,5	21,1 ± 11,5	18,1 ± 11,8	.48
HADS-D	2,2 ± 2,6	2,5 ± 2,6	2,1 ± 2,1	.73

Note. Values are Mean ± SD; p-values are based on ANOVA unless otherwise specified; Prior computer use based on 7-point scale (from 1= less than once a month to 7= more than 4 hours a day); Level of education based on 7-point scale (from 1= unfinished primary school to 7= university); FS= frequent switching experimental group; IS= infrequent switching experimental group; MT= mock training group; TICS= Telephone Interview for Cognitive Status; CIS-F= Checklist Individual Strength - Fatigue subscale; HADS-D= Hospital Anxiety Depression Scale - Depression subscale; [a] = *p*-value based on χ^2.

Intervention

Average number of completed training sessions was 57.1 (28.6 hours) and this did not differ between training groups (*F*(2,135) = .438, *p* = .65). All three groups improved equally on all training tasks, judging from the z-scores (*F*(2,135) = .192, *p* = .826), though in terms of total gain, the experimental conditions improved significantly more than did the active control (*F*(2,135) = 6.698, *p* = .002). Although the active control condition was asked to maintain a single game level for a set week, we discovered that many active control participants continued playing beyond this level, thus diminishing differences in adaptiveness between our training groups. It appeared that 42% of control participants played more than 10% of their training time beyond the highest allowed level (level 9), and 26% played more than 30% of their time beyond this level. Besides this, 25 subjects (39% of IS subjects, 21% of FS subjects) scored a maximal number of points at the highest possible level on one or two of the nine games, thereby compromising adaptiveness among both experimental groups. Although many of these cases occurred only in the last few weeks of the training period, these events may have led to suboptimal differences between the mock training and the experimental conditions.

Subjects were told after participation that we had made use of two conditions: one of which we expected would be less effective than the other. When asked whether they believed they had been in the more effective or less effective condition, participants were more likely to assume they had been in the experimental condition: 71% of FS and IS and 59 % of MT expected they had received our more effective training. Neuropsychological assessors did not guess subjects' training group above chance level, both before training (39%; $\chi^2(4, N = 105) = 2.73$, $p = .60$) and after training (33%; $\chi^2(4, N = 105) = 4.07$, $p = .39$). We can therefore assume that both neuropsychological assessors and participants themselves remained blind to the training conditions. Besides this, there was no difference between the three conditions in the perceived difficulty or enjoyment of the games, self-rated cognitive enhancement, or the degree to which they would like to continue playing the games (all *p*'s >.28), showing that all interventions were enjoyed equally.

Transfer effects

The statistics of the primary and secondary analyses reported below are detailed in Table 2. Main effects of Group were absent throughout and will not be discussed further. ANCOVA outcomes are reported where appropriate.

Table 2. Transfer Results

	Group												Comparison											
	FS (n=56)				IS (n=33)				MT (n=50)				time				group				time * group			
Measure	**Pre-training**		**Post-training**		**Pre-training**		**Post-training**		**Pre-training**		**Post-training**		**df**	**F**	**p**	η_p^2	**df**	**F**	**p**	η_p^2	**df**	**F**	**p**	η_p^2
	M	s.d.	M	s.d.	M	s.d.	M	s.d.	M	s.d.	M	s.d.												
Principal																								
Switch task	-348	175	-276	155	-368	266	-298	143	-367	225	-321	172	1;130	16,13	<.001	.11	2;130	0,238	.79	.004	2;130	0,535	.59	.01
Dual task	-1215	274	-1122	264	-1241	302	-1141	223	-1290	300	-1210	328	1;130	40,96	<.001	.24	2;130	0,702	.50	.01	2;130	0,078	.93	.001
SSRT	-258	48	-243	61	-269	56	-251	63	-265	61	-259	59	1;120	4,277	.04	.03	2;120	0,782	.46	.01	2;120	0,304	.74	.01
N-back	-10.2	7.4	-8.3	4.9	-9.2	4.5	-8.3	8.0	-11.4	7.8	-9.1	6.2	1;125	4,955	.03	.04	2;125	0,865	.42	.01	2;125	0,218	.80	.003
Secondary																								
D-KEFS TMT-4	-86.0	27.8	-80.7	31.0	-87,1	30,1	-71,1	22,1	-88.0	34.0	-77.8	31.7	1;133	16,796	<.001	.11	2;133	0,299	.74	.004	2;133	1,387	.25	.02
TMT-B	-71,7	29,3	-61,8	20,0	-72,6	31,7	-64,1	20,4	-71,3	21,0	-63,4	17,1	1;120	31,211	<.001	.21	2;120	0,312	.73	.01	2;120	0,519	.60	.01
Sem. fluency switch	-3,2	4,1	-3,6	4,2	-2,9	3,5	-5,3	4,5	-4,8	5,2	-4,8	4,1	1;129	3,653	.06	.03	2;129	2,362	.10	.04	2;129	1,66	.19	.03
Drag-and-drop	-37,3	9,7	-34,8	9,2	-39,2	8,5	-33,7	6,3	-42,6	17,1	-36,1	7,9	1;119	17,399	<.001	.13	2;119	1,877	.16	.03	2;119	1,289	.28	.02
Drag-to-grid	-62,8	13,5	-57,8	11,8	-66,4	13,1	-59,3	9,1	-65,3	12,2	-58,6	10,6	1;120	58,206	<.001	.33	2;120	0,535	.59	.01	2;120	0,706	.50	.01
Click task	-30,7	12,6	-27,3	8,2	-29,9	13,5	-26,0	6,0	-30,0	12,8	-25,2	7,1	1;118	12,549	.001	.10	2;118	0,333	.72	.01	2;118	0,159	.85	.003
TMT-A	40,6	11,3	37,4	7,0	42,9	10,4	36,7	8,6	43,9	15,2	37,4	7,7	1;119	27,518	<.001	.19	2;119	0,713	.49	.01	2;119	2,137	.12	.04
D-KEFS TMT-5	-28,1	9,6	-27,3	10,3	-26,2	7,9	-25,8	9,8	-27,8	9,5	-26,8	8,5	1;136	2,135	.15	.02	2;136	0,405	.67	.01	2;136	0,093	.91	.00
DSC	66,4	12,8	69,6	14,0	66,4	13,6	68,5	12,5	65,8	13,0	68,6	13,8	1;136	20,666	<.001	.13	2;136	0,054	.95	.001	2;136	0,255	.78	.00
DSC online	37,9	5,3	40,0	6,3	37,5	4,7	40,0	4,5	37,2	4,9	39,9	4,9	1;108	66,755	<.001	.38	2;108	0,082	.92	.002	2;108	0,498	.61	.01
ToL	33,5	23,3	27,1	17,9	33,4	21,4	22,4	15,9	37,0	24,4	22,3	19,1	1;123	24,059	<.001	.16	2;123	0,302	.74	.01	2;123	1,392	.25	.02
RPM	18,3	1,6	17,8	1,8	18,2	1,7	18,8	1,4	18,2	1,5	18,3	1,5	1;129	0,05	.82	.00	2;129	0,929	.40	.01	2;129	3,378	.04	.05
Shipley	15,3	2,8	15,9	3,0	15,8	2,7	17,1	2,5	15,8	2,7	16,5	2,7	1;130	23,496	<.001	.15	2;130	1,193	.31	.02	2;130	1,001	.37	.02
Corsi online	5,8	1,2	5,9	0,9	5,9	1,5	5,9	1,2	5,6	1,2	5,9	1,0	1;122	0,573	.45	.01	2;122	0,290	.75	.01	2;122	0,297	.74	.01
PASAT	96,7	16,5	103,5	16,2	96,6	14,6	103,6	11,2	93,8	16,5	101,2	13,5	1;133	67,008	<.001	.34	2;133	0,683	.51	.01	2;133	0,13	.88	.00
OSPAN	52,5	13,8	54,3	13,1	51,9	12,2	54,3	15,9	53,4	10,8	56,9	10,6	1;89	3.690	.06	.04	2;89	0,324	.72	.01	2;89	0,188	.83	.00
LNS	10,3	2,2	10,4	2,5	9,9	2,4	10,5	2,6	10,2	2,4	10,6	2,4	1;136	4,663	.03	.03	2;136	0,081	.92	.001	2;136	0,478	.62	.01
RAVLT	47,6	9,5	49,2	10,2	45,5	9,1	48,1	9,8	46,1	9,4	48,1	8,8	1;131	11,854	<.001	.08	2;131	0,435	.65	.01	2;131	0,219	.80	.00
RAVLT delay	10,6	3,1	11,1	3,0	9,3	2,9	10,0	3,2	10,4	2,8	10,6	2,8	1;131	5.744	.02	.04	2;131	1,853	.16	.03	2;131	0,599	.55	.01
Sem. fluency	23,4	4,8	23,4	5,7	22,6	4,6	24,1	5,3	23,8	5,1	23,2	5,2	1;129	0,487	.49	.00	2;129	0,014	.99	.001	2;129	2,146	.12	.03
Letter fluency	47,4	13,1	47,8	13,1	43,8	12,2	43,9	11,4	44,4	10,9	44,6	10,9	1;130	0,13	.72	.00	2;130	1,408	.25	.02	2;130	0,011	.99	.00

Note. p-values are based on repeated-measures ANOVA; Bonferroni-corrected significant values in bold; ηp2= partial eta squared (effect size); FS= frequent switching experimental group; IS= infrequent switching experimental group; MT= mock training; SSRT= stop-signal reaction time; D-KEFS= Delis-Kaplan Executive Function System; TMT= Trail Making Test; sem.= semantic; DSC= Digit Symbol Coding; ToL= Tower of London; RPM= Raven's Progressive Matrices; PASAT= Paced Auditory Serial Addition Test; LNS= Letter Number Sequencing; RAVLT= Rey Auditory Verbal Learning Test. TMT A & B, DKEFS 4 & 5, Drag-and-drop, Drag-to-grid and Click task in sec.; switchtask, dual task, SSRT in msec.; N-back in % correct

Principle analysis: Executive Functions

On task switching, all three groups significantly improved their scores over Time, but a Time * Group interaction did not reach significance. A similar pattern was seen on the dual task, with a main effect of Time that was not modulated by Group. This time effect disappeared when correcting for the number of workouts ($F(1,128) = .721$, $p = .397$, $\eta_p^2=.006$). Time effects for N-back and Stop-signal task did not survive Bonferroni correction, and no modulation by Group was found. Equivalent results appeared when outliers were included.

Secondary analysis

Most of the secondary measures were subject to improvement with Time, as described below, but none of these effects were modulated by Group. Performance on 2 out of 3 cognitive flexibility tasks improved over time for all three groups. Both the DKEFS TMT and the online version of the TMT-B showed decreased switching latency. No significant effects were found for performance on the switch condition of the semantic fluency task. Psychomotor speed improved on the online TMT-A and the three mouse ability tasks (Click, Drag-and-drop, and Drag-to-grid). The motor speed condition of the DKEFS TMT did not show a significant Time effect. Processing speed improved in both the original DSC as the online version of the task. A significant Time effect was found for the ToL. In the reasoning domain, a significant Time effect was observed for the SILS. The score on the RPM did not change significantly. On tasks of working memory, both PASAT and RAVLT-direct improved over Time, whereas no change appeared on the online Corsi or the Operation Span. The score on the LNS was not significant after Bonferroni correction. No Time effect was found on long term memory measured with the RAVLT-delay. Finally, both semantic and letter fluency did not improve over Time for any of the groups. With outliers included in the data, the results showed the same pattern.

All Time effects disappeared when correcting for age, baseline TICS score, number of completed training sessions, or education level, regardless of whether one or multiple covariates were used.

Follow-up effects

As specific training effects were lacking, T1 measurements were not examined. An explorative repeated-measures ANOVA was run for tasks which did exhibit a significant Time effect and had also been administered at T3. All of these measures improved even further on T3, revealing higher effect sizes for all tasks (Switch task: $F(1,125) = 59.167$, $p < .001$, $\eta_p^2 = .32$; ToL: $F(1,115) = 37.237$, $p < .001$, $\eta_p^2 = .25$; online DSC: $F(1,100) = 101.421$, $p < .001$, $\eta_p^2 = .50$; TMT-A: $F(1,112) = 43.755$, $p < .001$, $\eta_p^2 = .28$; TMT-B: $F(1,112) = 53.234$, $p < .001$, $\eta_p^2 = .32$; Click task: $F(1,112) = 16.933$, $p < .001$, $\eta_p^2 = .13$; Drag-and-drop: $F(1,109) = 39.465$, $p < .001$, $\eta_p^2 = .27$; Drag-to-grid: $F(1,113) = 60.085$, $p < .001$, $\eta_p^2 = .35$). However, these Time effects did not interact with Group for any of these measures, and no Time effects remained when correcting for age, education level, baseline TICS score, and number of completed training sessions, regardless of whether one or multiple covariates were used.

Extra analyses

We added an extra analysis, examining a possible interaction between Time, Group, and switch task trial type (switch- and non-switch trials). This three-way interaction was not significant ($F(6,360) = 0.233$, $p = .943$, $\eta_p^2 = .004$).

To examine whether there was a significant difference in training benefit of Group after adjusting for baseline performance, we ran a separate number of ANCOVA's using difference scores on all measures, including baseline scores as a covariate. There was a difference in score on the Raven's Progressive Matrices ($F(2,128) = 4.111$, $p < .019$, $\eta_p^2 = .060$) between the frequent- and infrequent switch conditions, when adjusting for baseline RPM score. However, this value did not survive Bonferroni correction.

DISCUSSION

We investigated the possibility to train cognitive functioning in older adults using a computerized cognitive training. For this purpose, we designed an intervention with multimodal, novel, adaptive training tasks, a built-in element of flexibility, and frequent training sessions to optimize transfer, and selected a number of transfer tests with parallel forms to minimize retest effects. Based on previous literature (Mahncke et al., 2006; Karbach & Kray, 2009; Düzel et al., 2010) we expected far transfer to several executive functions. Improvement over time was found on training tasks as well as on multiple transfer tasks covering all domains. Our primary analyses showed that older adults benefited from training across the main domains of executive function (updating, shifting, inhibition; Miyake et al., 2000). Our secondary analyses partially confirmed these findings: improvements were seen in planning, reasoning, two out of three cognitive flexibility tests, two out of five working memory tests, and two out of three psychomotor speed tests; while no improvement was observed for IQ, long-term memory, and fluency. Improvements were further amplified 4 weeks after training completion.

Most importantly, however, the experimental training that capitalized on flexibility, novelty and adaptiveness as central features did not lead to more progress than the trainings without these elements. This suggests that there was no additional advantage of these key ingredients in training tasks, and that improvements were induced mainly by other causes.

On outcome measures where a covariate was included, all time effects disappeared. Although covariates were added only if a significant correlation with a measure occurred, on plotting the covariate data it appeared that different values of each covariate affected the various measures differently. This suggests that the covariation effects were not systematic across covariates, and therefore did not add to the model to explain training effects.

Our study had a number of limitations, some of which it shares with similar studies in the literature.

Generic Factors: Motivation, Expectation, and Placebo Effects

The effects on training benefits from training-nonspecific factors such as attention, motivation, expectancy, and placebo may have played a larger role than anticipated. Long-term intensive training interventions are accompanied by degrees of personal attention as well as motivation that in themselves may suffice to enhance cognitive performance. Moreover, such programs may induce an expectancy to improve, which has proven to generate powerful placebo effects across a wide range of domains and paradigms (Boot et al., 2013; Dougherty et al., 2016; Foroughi et al., 2016).

Thus, one explanation also for the present set of findings is that of a placebo or subject-expectancy effect. In the information booklet that aspirant participants received at the beginning of the study, we informed them about our intention to investigate whether benefit from training was a possibility, and stated our hope to find positive effects on cognitive functioning. Although it also explained that we were not sure whether this would be the case, we might have inadvertently given subjects the notion that we expected benefit, thus leading them to put extra effort in post-training performance. The finding that a majority of our participants had assumed to be in the experimental condition, may support this notion. A similar pattern has been observed in (Foroughi et al., 2016), in which subjects who had responded to a suggestive flyer displayed more improvement on cognitive functions, compared to a control group responding to a non-suggestive flyer. Elsewhere, we will report on how participants perceived their progress subjectively. If a subject-expectancy or placebo effect has indeed influenced the current results, these improvements might appear in their subjective reports, shedding more light on the question of overall time-based improvement.

A similar, but slightly different interpretation is that of the Hawthorne effect (Green & Bavelier, 2008), referring to subjects’ tendency to perform better on tasks when they are working towards a common goal or when a need for attention is satisfied by participating in research. In our case, as all three conditions received a certain amount of social stimulation, this might have led to increased motivation to perform well on the post-training measurements.

Potential Limitations: Challenge Levels, Group Composition, and Social Cohesion

Based on previous studies using computerized training (Basak et al., 2008; van Muijden et al., 2012; Ballesteros et al., 2014; Kuhn et al., 2014), we assumed that using the current set of nine games—with 20 levels each—would provide ample variation and challenge for 12 weeks. Nonetheless, some evidence suggests this challenge was not always met in our experiment. First, a considerable number of participants found themselves reaching the maximum score for at least one of the games within a number of weeks before the end of the training, diminishing adaptiveness in these groups. In addition, on the exit questionnaire, some participants in the frequent switch training commented that the training was too simple or repetitive, or specifically criticized adaptiveness, reflecting that learning in the first half of levels was too gradual and in the second half too steep; we did not answer to all personal needs for challenge. An improvement for future studies is to implement more variable and novel activities tailored to individual demands to further optimize performance increases. Yet, by and large, most participants experienced the tasks as aptly challenging, with the levels of variability and adaptiveness contributing to that experience.

Training in our active control group, on the other hand, might have been too challenging. We had meant to generate novelty only in the frequent- and infrequent switching conditions, and assumed that by selecting only four, less multimodal, games in the active control condition, novelty would be minimal. However, for many participants (across groups) playing games seemed in itself to be a sufficiently novel activity to incur small cognitive effects. Many participants had not previously used a mouse in the relatively fast manner that was necessary in our games and computer tasks. The strong transfer effects to mouse ability tasks in all three groups supports this assumption. Another point to consider is that the limitation on adaptiveness in the control condition was compromised by the fact that many participants continued past the maximally allowed weekly game level, causing the control condition to be more challenging than intended. Thus, our control condition may have unintentionally targeted similar functions as in the experimental conditions. This is especially evident when comparing our design to those of other studies. Overall, many training studies that find more evident transfer than the current study have employed active control conditions that appear distinctly less active than the experimental conditions, spending fewer hours on assigned tasks and having markedly less interaction with the researchers. Some only use a passive control condition, or none at all. Our results stress the value of including an active control condition that receives equal attention and training time, yet creates no overlap in the engagement of functions.

Furthermore, for many of our subjects, participating in the training involved more than just playing the games and may have included aspects such as following a link in an email to get to the online test batteries, downloading a new browser, (later) starting up the correct browser, and navigating to the right page. Although all of our subjects used their computer regularly and knew about basic internet use, such actions beyond the training itself often exceeded those of their usual activities and, thus, may have constituted a type of unintended cognitive training.

However, results from our stroke sample, described elsewhere (van de Ven et al., 2017), suggest that this has had only a minor effect. In this sample, we investigated effects of the TAPASS training in recovering stroke patients, including a no-contact waiting list condition. This group showed equal improvements to the experimental intervention and active control, including mouse ability tasks. This suggests that playing games or increased use of a mouse could not have been the main factor behind the transfer effects that we found. Instead, the improvements in this study, appearing in all three training groups, are more likely to have been caused by retest effects. Almost all tests with parallel forms did not reach significance in any of the groups. Also, there was no indication that improvement was limited to specific cognitive processes, as transfer effects were not exclusive to specific domains. Testing frequency thus seems to be the most important factor underlying these time effects. Although we included parallel tests where available, future studies might benefit from using parallel tests only, to minimize these retest-effects. Furthermore, using the statistical analysis used at present, we have not fully been able to uncover further knowledge of the individual differences in training benefit. More thorough analyses are necessary to provide additional insight into the individual learning processes and contribute to future interventions.

Our design largely lacked social interaction with other participants, which might have provided additional stimulation (Ybarra et al., 2008; Charles & Carstensen, 2010). Also, although the focus for this project was on the effectiveness of the popular home-based training tasks, some recent evidence reveals that for non-impaired older adults, individual at-home training might not be as effective as group training (Lampit et al., 2014; Kelly et al., 2014) or training sessions provided in the lab (Basak et al., 2008; Lövdén et al., 2012; Ballesteros et al., 2014). Among reasons given are optimization of adherence and compliance, as well as providing motivation to master more difficult training tasks. Possibly, participants in these studies may have benefited more from the training due to this procedure, producing more conspicuous results than the home-based training method presented here. Yet, as we contacted participants frequently with motivational telephone calls, it is unclear whether increased transfer in the experimental conditions would have occurred, if subjects had received face-to-face support from a trainer instead.

In our current study, we used a set of commercially available games targeted at the general population to train their cognitive functions. Naturally, commercial- and scientific games are created with different intentions in mind, yet in this case, we expect this to be less of a concern, as we took care to adapt each game, as well as the design of the intervention, to fit our scientific objectives, with the additional benefit of generalising more to other functions than the frequently used commercial games.

A potential methodological limitation of this study was the homogeneity of our elderly sample, with a high educational level and relatively few cognitive complaints. This is characteristic of participants interested in volunteering in research experiments, increased further by the inevitable self-selection due to our inclusion criteria, such as the requirement to own a modern computer and to be willing to spend 12 weeks on our training. This raises the question to what degree cognitive improvement could have been attained in a sample with ample daily cognitive stimulation and minimal need to improve functions. A sample of older, less fit individuals might be more representative in displaying the benefit for the population. However, logistically it is difficult to encourage lower-educated, more cognitively impaired individuals to participate in research, let alone spend a sufficient amount of time on such an intervention. Despite subjects' demographic homogeneity, we noticed a large test score variability within groups, overshadowing any differences between them.

CONCLUSION

Our cognitive flexibility training, using elements based on previously effective cognitive interventions, did not produce the expected near- and far transfer. Although training benefits were observed almost across the board, equal effects appeared in the active control group. Taken at face value, our results with commercially available training games suggest that this type of training may yield cognitive benefits among older adults. In our experimental design, however, we could not disentangle training effects from those attributable to test practice, expectancy, and motivation. Our parallel study with recovering stroke patients (van de Ven et al., 2017), which included a wait list condition, suggests that such factors may well have overshadowed the beneficial effect of the training itself and that training effects on cognition could be rather small. Additional investigation into different training methods is advised, including stimulation of social interaction and the use of more variable, novel, group-based yet individual-adjusted activities. Our results further emphasize the importance of using parallel forms as outcome measures for transfer and including both passive and active control conditions.

As a future direction, we may observe that a thus far underexplored territory pertains to individual differences in ‘trainability’ or the susceptibility to benefits from particular aspects of a training. For instance, it may prove fruitful to explore which cognitive or neural connectivity profiles are predictive of who will improve in what domain. If brain training is to be successful in a meaningful way, we first have to learn more about which determinants are key in tailor-made interventions to maximize far transfer.

SUPPLEMENTARY MATERIAL 3.1

Rating of performance during task

In all groups, participants acquire gold stars on screen for their performance on each game. An overview of which stars have been obtained per level can be seen at the beginning and end of each game.

For the FS and IS groups, if subjects obtain zero or one star they are asked to maintain training on the same level of difficulty. If two stars are achieved, they are encouraged to select the next level, but also allowed to stay on the same level to try to obtain three golden stars. If three stars are acquired, they are asked to pick the higher level of difficulty.

The MT group was asked to always select the same level during training, and only continue to a new level at the beginning of the training week. In weeks 6 and 7, and in weeks 9 and 10, the same level was played for two weeks.

Supplementary Figure 1. Performance rating per game visible to participants.

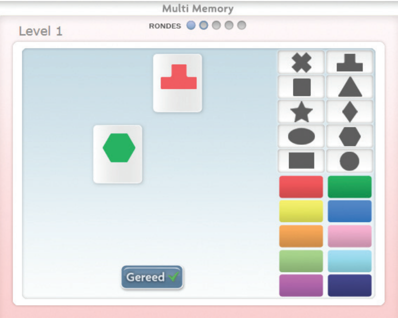
SUPPLEMENTARY MATERIAL 3.2

Description of Cognitive Training Games
Memory training

Toy Shop: A shopping list with pictures of items is shown for a limited amount of time. Participants need to recall the items to collect them from a shelf.

Multi Memory: Cards are shown for a limited time, with figures in different colors and shapes. Participants have to reconstruct these figures after they have disappeared.

Moving Memory: Comparable to the well-known game of Memory, participants need to find pairs of cards. In this variation, the remaining cards change position after a pair has been found. Figures on the cards can only be remembered based on the number printed on the back, but no longer by the location.



Supplementary Figure 2. Memory training games: Toy Shop, Multi Memory and Moving memory

- Cognitive flexibility training

Attention training

Mind the Mole: Molehills appear on screen one by one, each moving in a particular direction. Participants need to be vigilant for all molehills on screen and select one once it begins to move in a different direction before the mole takes away all the carrots.

Birds of a Feather: Under time pressure, participants have to count birds of a particular color and shape among other different birds.

Pattern Matrix: A number of tiles with different patterns on it are displayed. Participants need to mentally rotate the tiles to find all matching pairs within the given time.

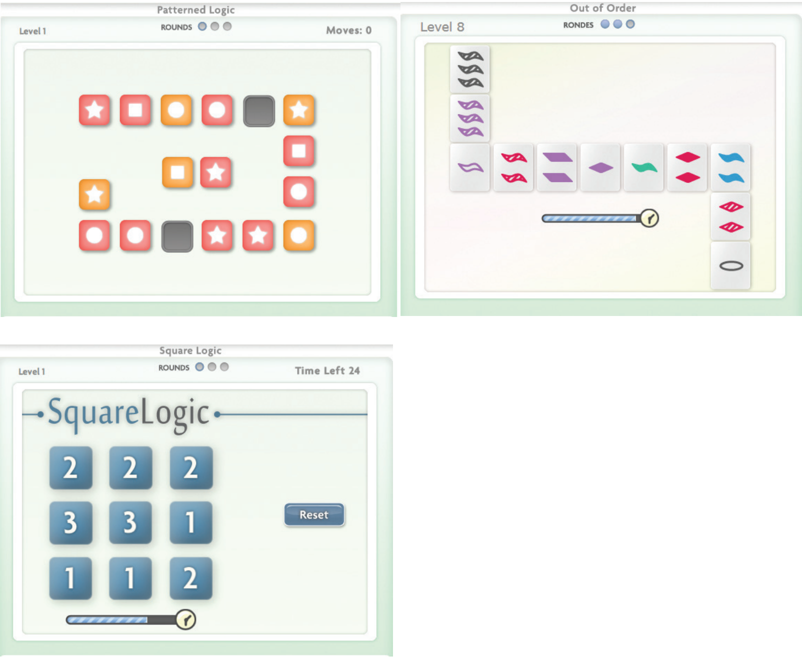
Supplementary Figure 3. Attention training games: Mind the Mole, Birds of a feather and Pattern Matrix

Reasoning training

Pattern Logic: A number of cards with figures on it are displayed in unknown serial patterns of color and shapes. Participants have to find the patterns and complete the missing tiles.

Out of Order: A row of tiles with figures in different shapes and colors need to be arranged under time pressure in such a way that they match with adjacent tiles on minimally one characteristic (e.g. color, shape, pattern or number of figures).

Square Logic: Cards containing a number have to be dragged on top of each other within the time given, such that only one block will remain. Cards can only be placed on adjacent cards with a number that is a count one higher or lower.



Supplementary Figure 4. Reasoning training games: Pattern Logic, Out of order and Square Logic

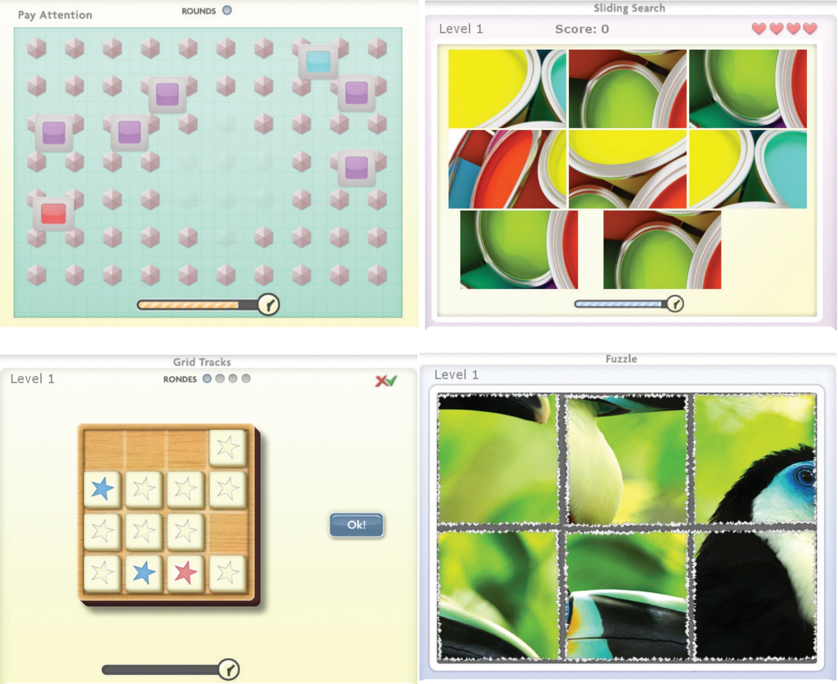
Active Control games

Pay Attention: Colored squares will appear randomly on the screen. Whenever the color of the square is changed, the participant has to select it as fast as possible.

Sliding Search: Pictures will slide from left to right over the lower part of the screen. Participants need to match pictures from the upper part with those in the lower part of the screen.

Grid Tracks: Participants have to mentally follow the trajectory of a number of tiles previously marked with a star. When the blocks stop moving, participants need to locate the stars from memory.

Fuzzle: Participants have to reconstruct a fractured picture within the given time.



Supplementary Figure 5. Active control games: Pay Attention, Sliding Search, Grid Tracks, and Fuzzle

Chapter 4

Does cognitive flexibility training enhance subjective mental functioning in healthy older adults?

Based on:

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ABSTRACT

Declining cognitive abilities in older adults can contribute to significant changes in socioemotional health and substantially reduce their perception of well-being. Whereas much attention has been dedicated to creating cognitive training programs to improve cognitive health in old age, there is little emphasis on the consequences of such interventions for subjective mental functioning. We created a randomized controlled trial in which we evaluated the effects of an adaptive computerized cognitive flexibility training. Healthy older adults (60-80 years old) were assigned to one of three conditions (frequent or infrequent switching or an active control group) and performed 58 half-hour sessions within a period of 12 weeks. We measured effects on subjective cognitive failures and executive dysfunctioning, everyday functioning, depressive symptoms, anxiety, and quality of life, before and after training. Additionally, participants' proxies rated their cognitive failures and executive dysfunctioning. Subjective cognitive failures and executive dysfunctioning improved 4 weeks post-training in all groups, although effect sizes were low (η_p^2=.058 and .079, respectively) and there were no differences between groups (all *p*'s >.38). No significant changes in these subjective reports were seen directly after training, and this was the case in all groups. Proxies did not report any functional changes over time, yet their evaluations were significantly more favorable than those of the participants themselves, both pre-training (p <.0005) and post-training (p=.004). Although we found no evidence of improvement on subjective mental functioning, we adduce several factors that encourage further research into the effects of computerized cognitive training on subjective performance.

INTRODUCTION

The world's population is aging rapidly. According to the latest estimates, between 2015 and 2050, the proportion of adults over the age of 60 will double, yielding a disproportionate percentage of older adults (World Health Organization, 2015). Normal aging is often characterized by a decline in cognitive functions, affecting cognitive control, processing speed, long-term memory, and other processes essential to independent daily life (Salthouse, 1996; Fisk & Sharp, 2004; Luo & Craik, 2008). Although emotional regulation and positive affect are often found to be increased in older adults (Charles & Carstensen, 2007), declining cognitive health can lead to a preoccupation with waning functional abilities, reduced social interactions, significant decreases in quality of life, and danger of depression (Jonker et al., 2009; Cacioppo et al., 2011; Pusswald et al., 2015).

In addition to objective decline in cognitive abilities, subjective cognitive complaints (Waldorff et al., 2009; Hohman et al., 2011), depression (Wilson et al., 2002; Green et al., 2003), and high levels of anxiety (Sinoff & Werner, 2003; Bierman et al., 2007) have also been noted as risk factors for subsequent cognitive decline and impairment, nursing home placement, and dementia. To assess this, subjective reports may be able to identify impending impairment at early stages, when clinical changes cannot yet be detected by neuropsychological tests (Jungwirth et al., 2008; Schultz et al., 2015; Molinuevo et al., 2017). It is, therefore, important to examine whether subjective well-being can benefit from a cognitive intervention. The present study aims to investigate the effects of computerized cognitive flexibility training on subjective cognitive, executive and everyday functioning, quality of life, depressive symptoms, and anxiety. We will refer to all these aspects throughout as subjective mental functioning.

In recent years, there has been increasing attention for the effects of cognitive training in healthy older adults (Lampit et al., 2014; Melby-Lervåg et al., 2016). Although training has in many cases led to significant improvements on laboratory tasks, the subjective effects of such interventions, such as effects on quality of life or daily functioning, are often overlooked. The focus of most training studies is on objective functional effects, rather than individual experience. However, subjective mental functioning could benefit from cognitive interventions in a number of ways, for instance by directly improving self-esteem (Burgener et al., 2008), daily functioning (Corbett et al., 2015), and quality of life (Wolinsky et al., 2006), or diminishing depressive symptoms (Allaire et al., 2013; Calkins et al., 2015a). Ultimately, for cognitive training effects to be meaningful and to influence older adults' independence, it is essential for such generalization to take place (Kelly et al., 2014). Hence, an intervention should not only improve cognitive functioning, but should preferably also affect subjective cognitive experience and daily functioning in the personal environment.

Thus far, results from interventions targeting subjective outcome measures are mixed. Improvement has been found after trainings of memory enhancement (Valentijn et al., 2005; Fairchild & Scogin, 2010; Preiss et al., 2010), group-based self-efficacy (Hastings & West, 2009; McDougall et al., 2010), and speed of information processing (Smith et al., 2009). Likewise, leisure activities and volunteer work seem generally beneficial (Tesky et al., 2011), especially affecting well-being (Souza et al., 2011; Kuykendall et al., 2015; Bureš et al., 2016). General training of computer or internet use, on the other hand, does not appear to have effects on quantitative subjective scales measured (White et al., 2002; Slegers et al., 2008), although participants in these training studies reported benefiting in more qualitative ways, such as in self-confidence and social aspects. In contrast, when computer use involves playing cognitive games, participants may benefit in several domains, such as cognitive failures, social connectedness and fewer complaints of depression (Hardy et al., 2015; Hausknecht et al., 2015). Whether subjective experience is altered by training thus seems to depend largely on the type of intervention given, with computer game training offering promising prospects of improving subjective mental functioning.

Conversely, it is evident from these results that effectiveness is also highly dependent on the domain of subjective measurement. For instance, benefits are often seen in memory complaints (Hastings & West, 2009; Fairchild & Scogin, 2010; McDougall et al., 2010; Tesky et al., 2011), subjective attention (Richmond et al., 2011), and quality of life (Wolinsky et al., 2006; Slegers et al., 2008; Hausknecht et al., 2015). In relation to activities of daily life, some studies find no effects (Ball et al., 2002; Slegers et al., 2008), whereas others do (McDougall et al., 2010; Corbett et al., 2015). Similarly, subjective cognitive functioning has been positively influenced by training (Smith et al., 2009; Preiss et al., 2010; Hardy et al., 2015), but this has not been reported consistently (Valentijn et al., 2005; Tesky et al., 2011). Finally, improvements in mood

(Slegers et al., 2008; Fairchild & Scogin, 2010; McDougall et al., 2010; Tesky et al., 2011) and self-efficacy (Slegers et al., 2008; McDougall et al., 2010) seem especially difficult to achieve.

Interpretations of subjective training results are rendered more difficult by the limited use of subjective measures in such studies, leading to possible subjective effects of most interventions not being detected. As an intervention's test battery generally includes higher numbers of objective than subjective measurements, this might be one reason why subjective effects often go undetected (McDougall et al., 2010; Richmond et al., 2011; Shatil et al., 2014). One important adjustment, then, would be to integrate the use of subjective measurements in future assessments of cognitive interventions. One other way to obtain a more reliable view on self-report questionnaire results is to administer the same questionnaires to a significant other or a next-of-kin family member (so-called proxies). Especially in older adults with commencing health- or cognitive problems, it could be useful to solicit the observation of a proxy (Neumann et al., 2000).

As noted in Chapter 3, cognitive flexibility is the ability to adapt one's mental processes to the demands of a changing environment, which is an essential executive function, important for cognitive as well as daily functioning. For this reason, we especially wanted to test whether capitalizing on cognitive flexibility within our training would result in stronger intervention effects than without this element. We therefore designed a state-of-the-art cognitive flexibility training, integrating adaptive, multimodal, novel training games and frequent sessions. In view of the importance of subjective perception of changes in cognitive health and well-being, we included several types of subjective measures, as well as proxy versions of several questionnaires.

First and foremost, as our intervention included the important element of cognitive flexibility, we focused on assessing intervention effects on subjective cognitive functioning. Accordingly, we included subjective measures of cognitive failures as well as of executive dysfunctioning. In addition to cognitive flexibility, due to the game-based nature of our training, both speed of processing and reasoning were factors present in both experimental conditions. Since processing speed has been seen to improve health-related quality of life (Wolinsky et al., 2006) and evidence from reasoning training points to effects on everyday functioning (Willis et al., 2006), we included these specific measures of quality of life and everyday functioning. Additionally, we incorporated a measure of depression and anxiety into our battery. Although mood has previously proven difficult to improve by cognitive training, including a computerized game training (Bureš et al., 2016), to our knowledge none of these interventions included components of flexibility. Cognitive flexibility has been found to be especially impaired in individuals suffering from depression and anxiety (Murphy et al., 1999; Gualtieri & Morgan, 2008; Marazziti et al., 2010), so that including flexibility as a main ingredient in the training might have important implications for these constructs. Because a significant portion of the elderly suffer from symptoms of fatigue (Avlund, 2010), it is possible that fatigue levels in our sample are affected by training 5 days a week for 12 weeks. For this reason, a measure of fatigue was included to explore whether participants' levels of fatigue in the experimental conditions were positively or negatively affected. Following previous literature (Floyd & Scogin, 1997; Hertzog & Pearman, 2013; Hulur et al., 2015), we also explored the correlation between subjective and objective executive functioning, and between metamemory and objective memory and depression.

The purpose of this study was to assess whether 12 weeks of cognitive flexibility training could lead to an improvement of subjective cognitive failures and executive dysfunctioning, everyday functioning, depressive symptoms, anxiety, and quality of life. First, we expected participants in the cognitive flexibility condition to demonstrate greater improvements, compared with a non-flexibility cognitive training and an active control group, on subjective cognitive failures and executive dysfunctioning, depressive symptoms and anxiety. The non-flexibility cognitive training was expected to display larger improvements compared to active controls. Second, based on previous research on measures of quality of life and everyday functioning (Wolinsky et al., 2006; Willis et al., 2006), both cognitive training conditions were expected to improve equally, yet more so compared with the active control condition. Third, we expected the cognitive flexibility condition to maintain improvement on subjective cognitive failures and executive dysfunctioning at four weeks post-training, and report higher subjective training improvements, compared to the non-flexibility cognitive training and the active control group.

METHODS

Our study involved a randomized controlled double-blind design, effects of which were assessed using an extensive battery of neuropsychological paper-and-pen tests, questionnaires, and computer tasks. Results are distributed over multiple publications. For a full detailed description of our methods, see Buitenweg et al. (2017).

Participants

We recruited participants between the ages of 60 and 85, who were willing and cognitively able to commit to participation in a 12-week computerized training program. Participants were excluded if they had previously used the training games, had current substance abuse, severe visual impairment or colorblindness, had suffered a stroke or TIA, or scored below 26 on the Telephone Interview Cognitive Status (TICS; Brandt et al., 1988). The final sample included 158 participants, who were randomly assigned to one of three conditions (frequent switching, infrequent switching, and mock training; described below). We used a minimization program (Minimpy; Saghaei & Saghaei, 2011) to reduce asymmetry within the groups over the factors age, gender, education, TICS score, and computer experience. Full written informed consent was given by all participants prior to participation. The study was approved by the local Ethics Committee of the University of Amsterdam and registered under number 2012-BC-2566. All procedures were conducted in compliance with the Declaration of Helsinki, relevant laws, and institutional guidelines.

Study Protocol

Upon inclusion into the project, participants were requested (though not obliged) to provide a proxy (a friend or family member) who would be willing to fill out three online questionnaires both before and after training. Participants then came to the university for neuropsychological assessment and training instructions and signed an informed consent form (time = T0). A subgroup of participants came in twice for an MRI scan as well. Results of neuropsychological tests and MRI scans are reported separately. A member of the research team provided participants with detailed training instructions, which they also received in the form of instructional videos and a booklet to view at home. Subjective experience was measured at home using several online questionnaires. The order of task administration at baseline and post-training was counterbalanced over participants. Each subject was assigned a member of the research team who offered motivation and stimulation during weekly or bi-weekly telephone calls and assisted with training-related technical and scheduling issues. Participants trained for half an hour a day, five times a week, on days and times of their choice. Log-in times were monitored, and an automatic reminder was sent if a subject did not log in for more than two days. A small online log was filled out daily before and after each training session, inquiring after participants' motivation and fatigue. After 12 weeks of training, the training portal was closed and participants completed all questionnaires again (time = T2). A selection of questionnaires was also administered after 6 weeks of training (T1), and 4 weeks after the last training session (T3). After this last assessment point, all participants received free access to all games on the training portal.

Intervention

We based our three training programs on the existing website *www.braingymmer.com*. Games on this site are aimed at the general population, but we modified selected games and tailored them to the needs of older participants, for example by allowing longer reaction times. The order of all games and sessions in the 12-week course was pre-programmed to provide participants with approximately 30 minutes of game play and to prevent participants from exclusively selecting their preferred games. Feedback after finishing the games and sessions was the same in all three groups.

Cognitive training

Based on our reading of the literature and on our experience with cognitive tasks in experimental studies with older adult participants, we selected nine games, divided over the cognitive domains working memory, reasoning, and attention, that we deemed optimal to maximize cognitive flexibility. To increase variability and flexibility, we programmed the order of the games in such a manner that two consecutive games were always from different domains. Games consisted of 20 levels of increasing difficulty. After each game, feedback on performance was given with up to three stars on the screen. To operationalize adaptiveness, participants were coaxed to a higher difficulty level each time two or three stars had been attained. Within the cognitive training, we differentiated between two groups: frequent switching and infrequent switching. In the frequent switching condition, participants played 10 games of 3 minutes each, forcing them to frequently switch between different tasks and functions, thus maximizing flexibility. In the infrequent switching condition, a training session consisted of 3 games of 10 minutes each, allowing for fewer switches between domains. In the first week of training, participants in both conditions played the games for 10 minutes each, to sufficiently familiarize themselves with the individual games. Total time spent on each game was the same for both groups after completing 12 weeks of training.

Mock Training

For the mock training (MT) we used fewer games than in the experimental conditions to reduce variability. Based on our reading of the literature, and on our experience with cognitive tasks in experimental studies with older adult participants, we selected four games that presented relatively little demand on cognitive control, yet were visually stimulating. To minimize flexibility, games in one session were played for 10 minutes each. Although higher levels could be played if stars were attained, we directed participants to stay on a specific level for one or two weeks, thereby reducing adaptiveness.

Outcome measures

Subjective measures

Health-related quality of life was assessed by the Short Form Health Survey (SF-36; McHorney et al., 1994). The SF-36 consists of 36 questions, which are divided into eight separate scales, of which the Z-scores were combined into two weighted sums with higher scores representing better quality of life. Separate scales are: Physical Functioning, Role Limitations due to Physical Problems, Bodily Pain, General Health Perceptions, Vitality, Social Functioning, Role Limitations due to Emotional Problems, and General Mental Health. These scales were summed into a physical component (PCS) and a mental component (MCS) as standardized scores for the general Dutch population (Aaronson et al., 1998). Internal consistency of this questionnaire is high, with only Social Functioning values dropping for older subgroups. Construct validity is good, though on the scales Social Functioning, General Health, and Vitality, rates drop for older adults (Sullivan et al., 1995). Test-retest reliability of all scales is good to excellent (Andresen et al., 1996).

The Cognitive Failure Questionnaire (CFQ; Broadbent et al., 1982) was used to measure subjective cognitive functioning. This questionnaire consists of 25 items on a 5-point Likert scale and a maximum score of 100, with higher scores denoting more subjective cognitive dysfunctions. The CFQ was administered to both the participant and their proxy. Participants additionally filled out this questionnaire on the follow-up 4 weeks after training. Test-retest reliability after 21 weeks and 12 months is high (Broadbent et al., 1982) and inter-item reliability is excellent (Bridger et al., 2013).

Subjective executive functioning was measured using the Dysexecutive Functioning Questionnaire (DEX; Burgess et al., 1996) included in the Behavioral Assessment of the Dysexecutive Syndrome (BADS; Wilson et al., 1996). This questionnaire includes 20 items on a 5-point Likert scale and a maximum score of 80, with higher scores representing more subjective executive dysfunctions. The DEX was administered to both the participant and their proxy. Participants additionally filled out this questionnaire on the follow-up 4 weeks after training. Internal- and retest reliability and ecological validity of this questionnaire is good (Burgess et al., 1998; Shinagawa et al., 2007).

Everyday functioning was assessed using the Lawton & Brody Instrumental Activities of Daily Living (IADL) scale (Lawton & Brody, 1988), consisting of eight questions on a four- to six-point scale. Scores were added up to a total, with a maximum of 22 denoting worst performance. Questions that were answered with ‘not applicable’ or ‘never carried out myself in my life’ were replaced with the average of the participants’ remaining items. This questionnaire was administered to both the participant and their proxy. This scale has a high retest reliability and medium validity (Graf, 2008). Sensitivity and specificity of this scale to identify individuals with cognitive impairment is medium to good (BarbergerÐGateau et al., 1992).

Depression and anxiety were measured using the Hospital Anxiety Depression Scale (HADS; Zigmond & Snaith, 1983), which includes 14 items on a 4-point scale, divided over the subscales Depression and Anxiety, each with a maximum score of 21. A cut-off score of 8 and above is found to be optimal to screen for possible cases in the population for both depression and anxiety (Bjelland et al., 2002). Both subscales have good retest reliability beyond 6 weeks (Herrero et al., 2003) and medium concurrent and predictive validity (Lisspers et al., 1997; Herrero et al., 2003).

The Checklist Individual Strength- Fatigue subscale (CIS-F; Vercoulen et al., 1997) was used to assess fatigue. This scale consists of 8 items, with scores ranging from 8 to 56. A score of 35 and above is regularly used as a cut-off to denote severe fatigue, leading to high sensitivity and specificity. Internal consistency and retest reliability are also high (Worm-Smeitink et al., 2017).

To assess subjective training-induced improvement after training, we designed an exit-interview with four items (attention, reasoning, memory and overall cognition) answered on a five-point Likert scale ranging from 1 (“Certainly not improved”) to 5 (“Certainly improved”). Although this measure is not validated, it serves as a necessary tool to judge the subjective notion of improvement related to the training. The four items were added to a total score for subjective improvement with a maximum of 20.

We administered a short questionnaire online before and after each daily training session to assess motivation experienced during the training. Participants rated ‘Training interest before session start’, ‘Motivation to perform well’ and ‘Enjoyment of today’s games’ on a seven-point Likert scale. Each rating was averaged over all sessions, and the three scores were summed into a total Motivation score with a maximum of 21.

Subjective memory problems were measured with a four-question interview, in which participants were asked about memory failures, and worries and hindrance related to these problems (van den Kommer et al., 2014). The four items were added to a total score with a range of 0 to 12.

Training performance

We calculated game- and domain high scores, highest level attained, and gain scores between the first and last session played. To obtain game high scores, we determined the percentage of the maximum possible score per level, and added up all levels to a total per game, and all scores within each domain for domain scores. Subsequently, we computed a mean training score for all three training groups separately and transformed these to Z-scores to be able to compare mock training and experimental training groups relative to each other.

Statistical Analyses

For the first hypothesis, a series of mixed-design ANOVAs was carried out with the total scores on the CFQ and DEX and subscales of the HADS as dependent variables, with group (frequent switching, infrequent switching or mock training) as the between-participants independent variable, and time points T0 (baseline) and T2 (post-training) as a within-participants independent variable. Two similar mixed ANOVAs were run for the second hypothesis, using the physical and mental component of the SF-36 and total score of IADL as dependent variables. For the third hypothesis, an extra mixed-design ANOVA was carried out for the DEX and CFQ on all four time points and subjective training-induced improvement on all time points from T1. All participants who completed the tasks at T2 were included in the main analyses. Additionally, a per-protocol analysis was run, including only participants who completed at least 50 sessions. As exploratory analyses, we added a repeated-measures ANOVA with CIS-F as a dependent variable, as well as correlations between subjective and objective executive functioning and between metamemory and objective memory and depression. In case of a significant effect, correlations would be computed between significant measures and age, TICS score, and workouts completed, to determine whether to add them as a covariate. Education level required nonparametric correlation analysis (Spearman's Rho); all other measures used Pearson's correlation coefficient. To explore the extent to which individual characteristics influenced training benefits, significantly correlated covariates were added to a repeated-measures ANCOVA of the primary and secondary measures. Outliers were detected using Grubbs' Extreme Studentized Deviation test (Grubbs, 1950). We ran analyses with and without outliers. Reported results are without outliers, unless otherwise specified. IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA) was used for all statistical analyses. Normality was checked using Shapiro-Wilk's test and by evaluating skewness and kurtosis. A p-value of .05 (two-tailed if not mentioned otherwise) was considered significant. Bonferroni corrections for multiple testing were used for all analyses. Greenhouse-Geisser corrected degrees of freedom were used whenever sphericity was violated, although for the purpose of legibility the original degrees of freedom are reported.

RESULTS

Of the 158 participants who completed baseline measurements, 19 dropped out for various reasons (see Buitenweg et al., 2017). Sustainers were significantly younger than dropouts (sustainers M= 67.77, SD 5.0; dropouts M = 72.3, SD = 7.8, t[20,134] = -2,454, p = 0.023). There were no differences in education level, gender, TICS score, or training group between the final sample and dropouts (all p's > .19). The final analysis was based on the 139 participants who completed both T0 and T2 (age 60–80, $M = 67.8$, 60.4% female, mean years of education 13.7). Before training, the three training groups did not differ in demographic variables or baseline subjective values (see Table 1). Mean number of sessions completed at T2 was 56, and this did not vary across groups. The frequent switch training and the mock training contained a higher number of participants than the infrequent switch condition, because participants receiving MRI scans were only assigned to either the frequent switch or mock training condition. As the IADL revealed a substantial ceiling effect, it was decided not to include this questionnaire in further analyses.

Table 1

Demographics and baseline measures

Measure	**FS (n=56)**		**IS (n=33)**		**MT (n=50)**		**Sign.**
	M	s.d.	M	s.d.	M	s.d.	*p*
Gender (% female)	64.3		63.6		54		.51
Age	67.8	5	67.9	5.4	67.6	5.1	.97
Level of education	5.9	0.9	5.8	0.7	5.9	0.9	.76
TICS Score	35.6	2.5	35.7	2.3	35.2	1.8	.51
Prior computer use	5.6	0.8	5.4	1.6	5.8	0.8	.11
SF-36 Mental	0.2	0.8	0.4	0.7	0.2	0.9	.45
SF-36 Physical	0.1	0.9	-0.2	1.0	0.2	0.8	.17
Cognitive Failure Questionnaire	31.3	11.7	32.4	11.8	28.9	11.6	.37
Dysexecutive Functioning Questionnaire	14.9	9.5	16.2	9.0	14.2	9.1	.60
Instrumental Activities of Daily Living	0.8	1.3	1.0	1.5	0.5	0.9	.19
HADS-Depression	2.0	2.1	2.6	2.6	2.1	2.1	.53
HADS-Anxiety	3.2	3.0	2.8	2.5	3.0	2.5	.77
CIS-Fatigue subscale	20	11.5	21.1	11.5	18.1	11.8	.48
Proxy [a]							
Cognitive Failure Questionnaire	24.5	12.8	23.5	11.6	24.7	13.1	.93
Dysexecutive Functioning Questionnaire	13.3	10.2	10.6	7.0	14.2	12.7	.41
Instrumental Activities of Daily Living	0.8	1.8	0.8	1.0	0.6	1.2	.83

Note. Lower scores represent better performance except on SF-36 and TICS; *p*-values of Gender based on χ^2, all others based on ANOVA; Sign. = Significance; FS = frequent-switching experimental group; IS= infrequent-switching experimental group; MT= mock training group; Level of education based on 7-point scale (from 1= unfinished primary school to 7= university); TICS= Telephone Interview for Cognitive Status; SF-36 = Short Form Health Survey-36; HADS= Hospital Anxiety Depression Scale; CIS= Checklist Individual Strength; Prior computer use based on 7-point scale (from 1= less than once a month to 7= more than 4 hours a day); [a] = $n_{FS} = 44$, $n_{IS} = 24$, $n_{MT} = 42$.

Intervention Effects

The statistics of the analyses reported below are detailed in Table 2.

For the first hypothesis, Time effects for the Cognitive Failure Questionnaire did not survive Bonferroni correction, and no modulation by Group was found. Results of the DEX and HADS Depression- and Anxiety subscales also did not reveal a significant Time effect or a Time x Group interaction. Thus, none of the groups reported any improvement regarding cognitive and executive functioning or depression. For the second hypothesis, no main effect of Time or a Time x Group interaction was found for the SF-36 Mental- and Physical subscales, suggesting none of the groups noted a gain in mental or physical health.

For the third hypothesis, in which we computed an additional mixed ANOVA for the DEX and CFQ on all four time points, more positive effects were found. Significantly different scores between time points were found on both the DEX, $F(3;372) = 7.60$, $p < .0005$; $\eta_p^2 = .058$ (see Figure 3), and the CFQ, $F(3;378) = 10.87$, $p < .0005$; $\eta_p^2 = .079$ (see Figure 2). Post hoc tests using a Bonferroni correction displayed a significant improvement on the DEX between baseline (T0) and follow-up (T3; $p = .001$) as well as between post-training (T2) and follow-up ($p = .001$) and mid-training (T1) and follow-up ($p = .002$). On the CFQ, this effect occurred between the same time points (T0 to T3: $p < .0005$; T1 to T3: $p < .0005$; T2 to T3: $p = .020$). There was, however, no main effect of Group, demonstrating that all groups equally improved across sessions, both on the DEX, $F(6;372) = 1.143$, $p = .38$, and the CFQ, $F(3;378) = 1.044$, $p = .40$.

The same analysis was conducted on the three time points (T1, T2, and T3) of subjective training-induced improvement. Results revealed significantly different scores between time points, $F(2;258) = 6.23$, $p =.004$; $\eta_p^2 = .046$. Post hoc tests determined an improvement from T1 to T2 ($p = .011$) and T1 to T3 ($p = .032$), though there was only a marginally significant interaction with Group, $F(4;258) = 2.26$, $p = .072$; $\eta_p^2 = .034$, which was mainly caused by a much lower score on T1 by the infrequent switching group.

As only 51% of participants had filled out the subjective memory scale at baseline, we could not adequately run a repeated measures analysis on this data. Thus, in Table 2, we only report the data collected on T2, which was completed by 135 participants. No difference was found between groups in

Table 2

Transfer Results

	Group												Comparison														
	FS (n=56)				IS (n=33)				MT (n=50)				time					group					time * group				
Measure	**Pre-training**		**Post-training**		**Pre-training**		**Post-training**		**Pre-training**		**Post-training**		**df**	**F**	η^2_p	**p**		**df**	**F**	η^2_p	**p**		**df**	**F**	η^2_p	**p**	
	M	s.d.	M	s.d.	M	s.d.	M	s.d.	M	s.d.	M	s.d.															
Cognitive Failure Questionnaire	31.3	11.7	28.4	12.4	32.4	11.8	31.5	13.6	28.9	11.6	28.1	11.9	1;132	5.093		.03	.04	2;132	1.016		.37	.02	2;132	0.513		.60	.01
Dysexecutive Functioning Questionnaire	14.9	9.5	14.9	10.1	16,2	9.0	14.8	8.9	14.2	9.1	14.3	9.7	1;130	0.616		.43	.00	2;130	0.293		.75	.00	2;130	1.825		.17	.03
SF-36 Physical	0.1	0.9	0.2	0.8	-0.2	1.0	-0.2	1.1	0.2	0.8	0.2	0.7	1;133	0.134		.72	.00	2;133	2.134		.12	.03	2;133	0.301		.74	.00
SF-36 Mental	0.2	0.8	0.3	0.9	0.4	0.7	0.5	0.6	0.2	0.9	0.1	0.9	1;133	0.116		.73	.00	2;133	1.19		.31	.02	2;133	0.508		.60	.01
HADS-Depression subscale	2.0	2.1	1.7	1.8	2.5	2.6	2.1	2.1	2.1	2.1	2.1	2.2	1;131	1.483		.23	.01	2;131	0.568		.57	.01	2;131	0.077		.93	.00
HADS-Anxiety subscale	3.2	2.9	2.7	2.4	2.8	2.5	2.5	2.5	3.0	2.5	3.2	3.1	1;133	0.795		.37	.01	2;133	0.288		.75	.00	2;133	1.432		.24	.02
Memory scale (T2) [a]	n.a		9.8	3.2	n.a		9.1	3.6	n.a		9.2	3.7	n.a					2	1.177		.56		n.a				
Motivation scale (T2) [b]	n.a.		15.3	3.0	n.a.		15.4	2.2	n.a.		15.3	3.2	n.a.					2;138	0.027		.97		n.a.				
Subjective improvement (T2) [b]	n.a		13.11	3.4	n.a		13.1	3.6	n.a		13.2	3.6	n.a					2;134	0.005		.99		n.a				
Proxy [c]																											
Cognitive Failure Questionnaire	24.5	12.9	23.1	15.7	23.5	11.6	21.6	11.8	24.7	13.1	25.5	15.0	1;88	0.705		.40	.01	2;88	0.365		.69	.01	2;88	0.393		.68	.01
Dysexecutive Functioning Questionnaire	13.3	10.2	12.2	10.9	10.6	7.0	10.2	7.9	14.2	12.7	15.8	13.0	1;85	0.056		.81	.00	2;85	1.079		.34	.03	2;85	0.611		.55	.01

Note. Lower scores represent better performance except on SF-36; *p*-values are based on repeated-measures ANOVA unless otherwise specified; ηp^2= partial eta squared (effect size); FS = frequent-switching experimental group; IS = infrequent-switching experimental group; MT = mock training; SF-36= Short Form Health Survey-36; HADS= Hospital Anxiety Depression Scale; T2= post-training measurement; [a] = analysis based on Kruskal-Wallis; [b] = analysis based on ANOVA; [c] = *nFS* = 44, *nIS* = 24, *nMT* = 42.

reports of memory problems, motivation, or subjective training improvement. Participants' proxies did not report significant changes in cognitive or executive functioning over time, and there was no difference between groups. Results of these measures did not change when including outliers.

Everyone improved on the training tasks, as seen from the gain scores, although mean gain was significantly higher in frequent- and infrequent switch groups compared to the mock training, F(2,135) = 6.69, $p < .002$, as expected due to adaptiveness of the former. Despite this training improvement, correlations between gain score or total mean training score and change in subjective functioning were not significant (all *r*'s between -.09 and .15). A similar pattern was observed for correlations with proxy reports (all *r*'s between -.02 and .04).

Per-protocol analyses

Main analyses were repeated for participants who completed a minimum of 50 sessions. Eight participants were excluded (1 active control participant, 4 participants from the frequent switching condition and 3 from the infrequent switch condition), resulting in a final sample of 131 participants ($n_{FS} = 52$, $n_{IS} = 30$, $n_{MT} = 49$). Participants who had completed less than 50 training sessions did not differ on subjective baseline scores or demographic variables from the rest of the sample. Per-protocol training results were similar to the main analyses (see Table S1), indicating that participants who completed at least 50 sessions did not improve more on subjective mental functioning than participants who did not.

Exploratory questions

Although neither participants nor their proxies noticed significant changes over time, proxies' scores appeared much more favorable than the self-ratings. We performed an exploratory independent t-test on data of both time points to examine whether this difference was significant. CFQ ratings on baseline were higher (signifying more dysfunctions) in participants (*M* = 30.71, *SE* = 1.0) than in proxies (*M* = 24.35, *SE* = 1.2), which was significant, t(247) = 4.123, $p < .0005$, *d* = 0.52. Post-intervention, the same effect between proxies (*M* = 23.69, *SE* = 1.5), and participants (*M* = 29.01, *SE* = 1.1) appeared, t(225) = 2.947, *p* = .004, *d* = 0.39. On the DEX, participants' self-ratings on baseline were higher (*M* = 14.96, *SE* = 0.8) than those of proxies (*M* = 13.03, *SE* = 1.0), which was also the case after the training (*M* = 14.65, *SE* = 0.8; *M* = 13.10, *SE* = 1.2) although this difference was not significant.

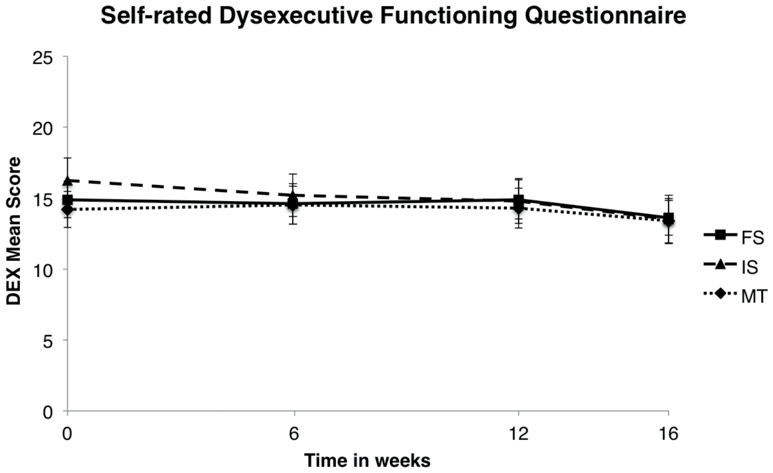

Figure 1. Dysexecutive Functioning Questionnaire mean scores, as a function of training and time (in weeks). FS = frequent switching; IS = infrequent switching; MT = mock training.

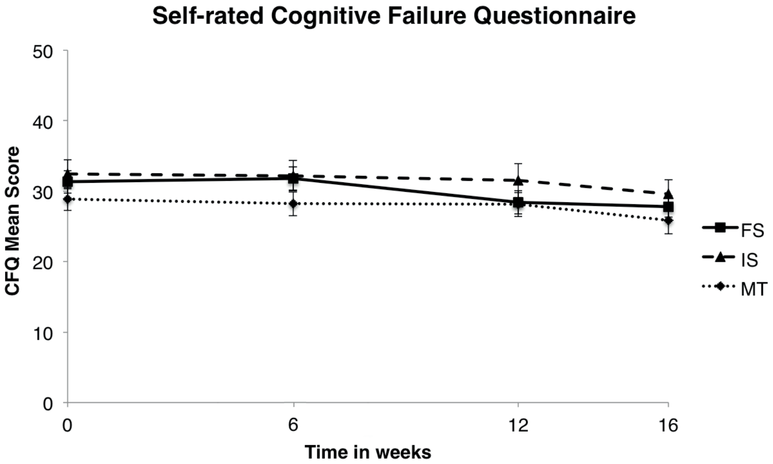

Figure 2. Cognitive Failure Questionnaire mean scores, as a function of training and time (in weeks). FS = frequent switching; IS = infrequent switching; MT = mock training.

We explored whether participants showed altered fatigue after the training. Repeated measures analysis of the CIS-fatigue subscale showed no alteration over time, $F(1,133) = 2.09$, $p = .15$, $\eta_p^2=.02$, and no effect of Group, $F(1,133) = 0.55$, $p = .58$, $\eta_p^2=.01$.

To test whether the relationship between subjective and objective memory and depression is similar to that found in previous research (Hertzog & Pearman, 2013; Hülür et al., 2015) we computed an exploratory Pearson's correlation coefficient between scores on our subjective memory scale, the HADS-D, and objective score on verbal long term memory (RAVLT delay; see Buitenweg et al., 2017). In accordance with the literature, we found a significant correlation between metamemory and depression ($r = .358$, n = 135, $p < .001$), whereas no significant correlations arose between metamemory and objective memory score ($r = -.063$). However, due to the low number of people in our sample reporting serious memory problems and the non-validated memory scale used, we must consider these results with care.

A similar issue concerns the question whether participants' subjective cognitive functions correspond to their objective cognitive task performances. To explore this, we computed a Pearson's correlation coefficient between baseline DEX and CFQ scores and primary executive functions performance (task-switching, dual tasking, updating and inhibition). Correlations between these measures were low and nonsignificant (DEX: all *r*'s between -.11 and .14; CFQ: all *r*'s between -.02 and .15).

DISCUSSION

In this randomized controlled study, we investigated the effects of a 12-week, computerized flexibility training on subjective cognitive and executive functioning, health-related quality of life, depression, and anxiety in older adults. Research into subjective effects of cognitive is scarce, and existing studies have rendered mixed results. Yet, as self-perceived cognitive functioning is an important prerequisite for healthy aging, we felt it essential to include these measures in our battery. No improvements were observed over time between the training groups and the active control when examined directly after training. Subjective cognitive and executive functioning increased four weeks after training, but no differential effect was seen between the intervention and control groups.

Our results suggest that including specific elements such as adaptiveness and cognitive flexibility in a computerized training is not sufficient to lead to noteworthy subjective effects immediately after training. This outcome replicates results from our stroke sample (van de Ven et al., 2017), in which we investigated subjective effects of the TAPASS training in recovering stroke patients. In this study, time effects on the DEX and CFQ appeared in all groups, including the no-contact waiting list condition. The findings also correspond with previous studies into computerized training (White et al., 2002; Slegers et al., 2008; Bureš et al., 2016), who found null results on a range of subjective measures. Conversely, our findings contradict those of Hardy et al. (2015), who found improvement on cognitive failures following training with similar games and study length to ours. A number of details are relevant to point out. First of all, in Hardy et al. (2015) participants of all ages were recruited, with the majority of ages in the young adult range. This may very well have led to faster or larger improvements than would have been seen in a strictly older population, and makes it more difficult to compare their results directly to ours. Secondly, after playing for a minimum of 15 minutes each day, participants in Hardy et al. (2015) were free to continue training with any of the available games. Self-selected able or enthusiastic subjects in that study might thus have been provided with (much) additional practice, likely leading to increased internal motivation, self-control, and self-perceived cognitive improvement compared with our study, in which participants were asked to adhere to a strict session schedule.

A similar situation applies to the results of Wolinsky et al. (2006), in which benefits for quality of life were found a number of years after speed of processing training. In many of our games, speed of processing certainly played a substantial role, yet no benefit to quality of life was observed. This could be due to the fact that in our intervention, speed of processing was a covert aspect of a broader training, whereas in Wolinsky et al. (2006) it was the main focus, providing participants with explicit strategies and examples for use in daily life. Besides, both Wolinsky et al. (2006) and Hardy et al. (2015) studied a very large sample of participants, allowing small differences between groups over time to stand out more easily than in our much smaller sample. With this in mind, it is important to realize that effect sizes in Hardy et al. (2015) were small, raising the question whether the results of this study can be generalized to performance in everyday life.

Regarding the sudden increase in subjective executive and cognitive functioning four weeks after training, there are several plausible explanations. First of all, there is the possibility that participants' reports on subsequent scales are affected by previous ones. However, we deem it unlikely that repeated measurements of this scale have caused a retest effect, as the retest reliability of both questionnaires is high (Shinagawa et al., 2007; Preiss et al., 2010; Bridger et al., 2013). Secondly, we need to consider objective improvement, which is not independent of subjective experience. In Buitenweg et al. (2017) we demonstrated cognitive improvement on a number of tasks following this training, including executive functioning. It is possible that participants only became consciously aware of general cognitive improvement until sometime after the training, therefore only reporting self-perceived changes until the post-training measurement. When asked explicitly about improvements brought on by the training, however, most subjects reported not noticing any changes in cognitive abilities. Similarly, a further increase in subjective training-induced improvement failed to appear after post-training, suggesting subjects' subjective reports of cognitive and executive performance would not have been conscious.

An unexpected finding was that participants rated their own cognitive performance in terms of failures as less favorable than their proxies. Although our results are confirmed by previous research on this topic (Burgess et al., 1998), many others report individual- and proxy ratings to be equal (Chan, 2001; Bogod et al., 2003). However, one must keep in mind that in most studies, proxy ratings are used in comparison to patient data, with proxies of dementia patients even rating them as worse than patients themselves (Howland et al., 2017; MacháĐová et al., 2018), whereas Burgess et al. (1998), like us, report on healthy adults. Also, the proxies in our study are rather heterogeneous, varying in the different proximities to the participant, and are thus somewhat less reliable. In this case, it seems likely that individuals have a more accurate insight into their cognitive failures than do their proxies, who might not notice every occasion a mistake is being made, especially as this is a healthy sample with little cognitive complaints. Yet, it is also possible that individuals simply overestimate their own failures, judging themselves too negatively.

Floyd & Scogin (1997) indicated that effect sizes of subjective cognitive measures after training are usually much lower compared to those of objective tasks and that the correlation between the two is generally small. Indeed, in our exploratory results, we did not find a correlation between subjective and objective tasks. Additionally, in an earlier publication, we reported improvement on several objective tasks in all groups after the current training (Buitenweg et al., 2017). Although still fairly low, larger effect sizes were seen than on the subjective measures. A plausible explanation for this occurrence is that the objective tasks used in our study were more sensitive to retest effects compared to the subjective questionnaires.

Numerous intervention studies have included measures of depression or mood to gauge change after training, yet most fail to find improvement on these factors (Wolinsky et al., 2006; Slegers et al., 2008; Fairchild & Scogin, 2010; McDougall et al., 2010). Likewise, our cognitive flexibility training also did not affect participants' depression levels. This could be due to the fact that depressive symptoms in our sample were low. There is some evidence that cognitive training could be of benefit to depressive symptoms in clinically depressed populations (Alvarez et al., 2008; Calkins et al., 2015), although these studies have only been done with younger adults. In older, clinically depressed populations, it is likely physical training might be more suitable to relieve symptoms (Blake et al., 2009), though to our knowledge, as of yet no effective cognitive training exists that indicates positive elevation of mood in older adults.

Regarding depression, we also observed a moderate correlation between depression scores and memory complaints, whereas a correlation between memory complaints and actual memory scores failed to appear, confirming earlier findings (Hertzog et al., 1990; Hertzog & Pearman, 2013; Hülür et al., 2015). One explanation is that feelings of mental distress or dysphoria affect individuals' judgment, causing negative thoughts about themselves to overshadow impartial perception. For instance, on the subjective memory scale, we asked about memory complaints and worries. Especially individuals who are prone to negativity might have reacted differently to these questions than if we had posed them in terms of more positive terms, such as memory capacity. Another interpretation is that many older adults are not well capable of judging their own memory abilities. (Crumley et al., 2014) argue that the ability to subjectively judge one's own memory capacity does not start until one's memory is actually declining, often in oldest-old adults, and that when assessing memory performance in a healthy sample of younger-old adults, the use of subjective measures should be discouraged. Indeed, in the current study, we included few oldest-old adults, and it's possible that without many actual memory failures, most were not able to accurately evaluate their daily memory performance. In future studies of subjective memory and depression, therefore, it is essential to also include individuals from the highest end of the age spectrum.

Some caution is required in judging the overall reliability of the questionnaire results. For instance, subjects were mostly free to complete the questionnaires at a time point of their choice, thus giving way to more external influences. Although access to the list of questionnaires was only granted from a specific moment onwards, due to the online nature of measurement, subjects were permitted three days or more to fill them out, possibly allowing unrelated events or fluctuations of mood and fatigue to affect their reports. This is backed up by Krueger & Schkade (2008) who argue that subjective well-being is often no more reliable than a typical mood questionnaire, as respondents inadvertently use arbitrary and transitory information, such as mood, to evoke an impression of their general well-being. Therefore, despite using reliable measures, we have to remember that subjective self-report questionnaires show feelings experienced at a given moment in time.

Another limitation of the current study is that the level of autonomy we offered participants was low. Loos & Zonneveld (2016) argue that a certain amount of pressure from a game or intervention can contribute to the experience of working towards a goal, while too much pressure is thought to lower motivation (Ryan & Deci, 2000). In our game protocol, in order to ensure all participants followed the same order and number of different games and time spent on each domain, we pre-programmed each training session to include the games in a specific order. It is possible that by preparing a set range of games for our subjects, we potentially eliminated participants' needed autonomy in all groups, thereby reducing overall internal motivation and enjoyment. Our previous comments on the training protocol in Hardy et al. (2015) apply here as well. One way to go about this in future studies is allowing for for self-pacing (Callahan et al., 2003) by granting participants more freedom in selecting the tasks and duration of engagement within each session, and relying more on their own capability for setting boundaries, possibly with use of reinforcement learning and feedback strategies (Green & Bavelier, 2008; Simon et al., 2010). It is not obvious, however, what the ideal balance is between motivating freedom of choice, on the one hand, and limitations imposed by experimental rigor, on the other.

Finally, participants in this study were high functioning older adults, which becomes evident from the self-ratings on cognitive failures and executive dysfunction and the ceiling-level subjective independence scores. This may have made it more difficult to achieve further improvement on the constructs measured here. In future research, stronger effects might be found in individuals with subjective cognitive complaints or Mild Cognitive Impairment.

In addition to the aforementioned, it remains important that future research focuses on identifying those subgroups for which specific interventions might be most effective. We further advise that in future studies of cognitive training in older adults, attention is paid to offering individuals certain guidelines to foster intervention effects, for instance in using strategies in daily life (Wolinsky et al., 2006). Finally, it is important that before the start of a training session, essential pre-training, such as practice on the training games, is given to enhance both training results and internal motivation (Floyd & Scogin, 1997).

The current study was designed to answer the question whether a commercially available, state-of-the-art, adaptive cognitive flexibility training could lead to improved self-perceived cognitive and executive functioning, quality of life, depression, and anxiety. Although 139 subjects each completed 58 half-hour sessions of brain training during 12 weeks, we found no evidence of advantageous outcomes to support this claim, though many questions remain. We strongly encourage further research into cognitive training effects on subjective performance, in order to be able to close these gaps in our knowledge.

Chapter 5

Spontaneous eye blinks predict executive functioning in seniors

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Buitenweg, J. I. V., Murre, J. M. J. & Ridderinkhof, K. R. Spontaneous eye blinks predict executive functioning in seniors. Submitted manuscript.

ABSTRACT

We investigated whether eye blink rate (EBR), a non-invasive, indirect measure of dopaminergic activity, could predict executive functioning (response inhibition, switching and working memory updating) and trainability in older adults. EBR was collected before and after a cognitive flexibility training, cognitive training without flexibility, or an active control. EBR predicted performance of both updating measures, as well as transfer of the interventions on one updating task. Individual inhibition and switching performance or training gain could not be predicted by EBR. Our findings tentatively indicate that EBR permits prediction of working memory performance in older adults. To fully interpret the relationship with executive functioning, we suggest future research should assess both EBR and DA receptor availability.

INTRODUCTION

Years of research into neurocognitive aging have demonstrated that with older age, cognitive functioning tends to decline, specifically in functions such as episodic memory, processing speed, and cognitive control, which are considered essential for unaffected daily functioning. Cognitive control, according to Miyake (2000) can be divided in the three dimensions of updating, shifting and inhibition, each of which show impairment with age (Fisk & Sharp, 2004). However, there is strong evidence that age *per se* is not the best predictor of this decline in functioning. Specifically, dopamine D2 receptor binding in caudate and putamen, which decreases with age (Rinne et al., 1993) is found to be more strongly associated with performance on tasks of episodic memory, processing speed, working memory and fluency than age (Bäckman et al., 2000; Erixon-Lindroth et al., 2005). Although age is generally negatively related to cognitive performance on various tasks, these results suggest that the individual rate of D2 dopamine binding in the striatum is able to better predict the degree to which these functions deteriorate.

As the world's aging population is growing, with increasing numbers of older adults expected to remain productive in the workforce, it is of great importance to have an affordable and reliable predictor of future decline in functions. Assessment of striatal dopaminergic activity could help in analyzing this relationship. One possibility is to use Positron Emission Tomography (PET) as an indirect assessment of dopamine components. PET relies on radioactive ligands that are inserted into the body and bind to dopamine receptors, which can then be localized and imaged. However, ligand-PET is an invasive and very costly procedure. One simple, non-invasive, and cheap method to reliably measure the connection between D2 dopaminergic function and cognitive control in older adults is spontaneous eye blink rate (Karson, 1983). EBR can be measured using various methods such as electrooculography (Colzato et al., 2008b), eye tracking (Dang et al., 2017) or video recording (Tharp & Pickering, 2011) and has been demonstrated to be a reliable predictor of D2 dopaminergic receptor density in the striatum (Jongkees & Colzato, 2016). Important evidence of this relationship is shown, first of all, in pathologies with dopaminergic dysfunction. For instance, EBR is reduced in patients suffering from Parkinson's disease, which is characterized by a depletion of dopaminergic nigrostriatal neurons (Deuschl & Goddemeier, 1998). Similarly, striatal D2 dopamine is significantly reduced in cocaine users (Volkow et al.,

1999) who also show a significant decrease in EBR (Colzato et al., 2008b). On the other hand, individuals suffering from schizophrenia, which is associated with elevated dopamine release at striatal D2 receptors (Brunelin et al., 2013), demonstrate increased EBR (Mackert et al., 1990). In addition, dopaminergic medication can be seen to influence EBR. Patients provided with dopaminergic D2 antagonists demonstrate a reversal of EBR to (near) normal levels (Mackert et al., 1990; Bologna et al., 2012), and in healthy humans, administration of dopamine D2 agonists increases EBR (Blin et al., 1990). Genetic evidence of the relationship between EBR and striatal dopamine comes from studies linking EBR to the DRD4/7 genotype, which is associated with the control of DA in the striatum (Dreisbach et al., 2005).

Moreover, EBR has been used to demonstrate functional differences in various tasks relying on dopamine functioning, such as the attentional blink (Colzato et al., 2008a), creative thinking (Chermahini & Hommel, 2010), probabilistic learning (Slagter et al., 2015) and cognitive control. For instance, in task switching, high blink rates are seen to correlate with improved accuracy (Zhang et al., 2015; Kleinsorge & Scheil, 2017) and increased flexibility (Dreisbach et al., 2005). Using a switch task with multiple conditions, the latter authors showed that in individuals with high EBR, switch costs are decreased when responding to novel targets, but increased when novel items posed as distractors, suggesting that increased flexibility comes at a cost of reduced stability, or distractibility. Further support for this claim comes from Müller et al. (2007) and Tharp & Pickering (2011).

By comparison, the relationship between EBR and inhibition is more ambiguous. For instance, increased EBR was shown to be correlated with longer stop-signal reaction time (SSRT), a measure of response inhibition (Colzato et al., 2009b). This association between higher dopamine levels and increased SSRT is backed up by a genetic study of the DRD4/7 genotype (Congdon et al., 2008). Yet, in regular cocaine users, known to exhibit a notably low EBR, SSRT is found to be impaired (Colzato et al., 2007). It is likely that the relationship between inhibition and striatal DA follows an inverted U-curve, representing optimal response inhibition with average amounts of dopamine, and is therefore highly dependent on the range of DA of the specific sample.

On the other hand, regarding the link between EBR and working memory, evidence points to an absence of association. For instance, no relationship is found between EBR and performance on the Operation Span (Tharp & Pickering, 2011) or a mental counters task (Zhang et al., 2015). This is supported by earlier evidence from a study in cocaine users (Colzato et al., 2009a) who are shown to perform equally to non-users on several different tasks of working memory. As inhibition is driven mainly by the nigrostriatal D2 pathway and working-memory updating by the mesocortical D1 pathway (Colzato et al., 2009a), most likely EBR is not a reliable predictor of functioning of the latter. Nonetheless, correlatory results from a 3-Back task (Zhang et al., 2015) reveal a negative relationship, suggesting decreased updating ability with higher EBR.

In sum, as the association between EBR and separate dimensions of cognitive control seems to vary with different tasks and samples, the relationship (be it linear or nonlinear) still remains somewhat controversial, demonstrating the need for further research with multiple tests in each domain.

Considering that dopaminergic systems decline with increasing age, it seems natural to assume that this would manifest itself as a decrease in EBR. Although one study indeed reports a significant decrease after age 40, which continues to decline with each decade of life (Chen et al., 2003), the majority finds no difference between EBR in young and older ages (Bentivoglio et al., 1997; Zaman et al., 1998; Kruis et al., 2016). A number of studies (Sun et al., 1997; Deuschl & Goddemeier, 1998; Sforza et al., 2008) even report a notable increase in EBR in 70 to 79-year-olds in comparison to middle aged adults, though most samples are small and the differences are not significant. As EBR and dopamine evolve differently with age, it is possible that the beforementioned association between EBR and dopamine is no longer valid in older ages. Still, a direct relationship would need to be determined more robustly in future studies measuring both EBR and dopaminergic function in older adults, before firm conclusions can be drawn.

Furthermore, not much is known about the relationship between EBR and cognitive functioning in healthy older populations. One recent study in older adults suggests that EBR is negatively related to cognitive functioning, as measured with a general clinical screening (Ladas et al., 2014). However, this sample consisted of both healthy older adults and individuals suffering from Mild Cognitive Impairment, the latter of which displayed a significantly higher

EBR, thus confounding the correlation. Given the lack of knowledge in this field, it remains important to examine the connection between EBR and cognitive functioning in older age. Due to the inter-individual variability within the older population (Christensen et al., 1999; Raz et al., 2010; Kanai & Rees, 2011) it is important to also study the individual differences between older adults rather than focus on the differences between age groups. For this reason, we initiated a study in healthy older adults in which we measured EBR along with several measures of cognitive control to gain more knowledge on this subject.

Recent attempts have been made to counteract the age-related decline using cognitive training (Karbach & Verhaeghen, 2014; Buitenweg et al., 2017). Improvements have been reported in various domains, such as working memory (Buschkuehl et al., 2008; Zinke et al., 2014), task switching (Karbach & Kray, 2009; Basak & O'Connell, 2016) and multitasking (Cassavaugh & Kramer, 2009). In young adults, increased DA release and functional activation in the striatum have been noted after training (Kühn et al., 2013; Bäckman et al., 2017) though this effect was not replicated in older adults (Dahlin et al., 2008). Multiple studies also show that dopamine activity in the striatum is associated with improvement in WM after training. For example, Dahlin et al. (2008) show that in young adults, generalisation of updating training to untrained tasks of working memory (known as transfer) is dependent on striatal activity. Using individual differences in dopaminergic D2 levels to predict training success could add to our knowledge on who benefit from different types of interventions. In young adults, baseline striatal grey-matter volume has been shown to be associated with later training improvement on a strategic video game (Erickson et al., 2010), with dorsal striatum specifically predicting performance on a game engaging cognitive flexibility. This suggests that the striatum plays a key role in learning from flexibility training, and that individual differences in volume or activation can predict later training success. Yet, this still leaves open the question whether this extends to transfer from training. Also, so far such a paradigm has not yet been investigated in older adults. If EBR could serve as a predictor of future decline as well as potential training advantages in older ages, this would offer a substantial benefit to society. Therefore, we will additionally study the question whether susceptibility for training benefit is dependent on individual differences in striatal D2, as measured by EBR.

There is evidence that the link between individual differences in executive functions on the one hand, and EBR on the other hand, can be modulated by polymorphisms, such as Val158Met (Colzato et al., 2010) affecting dopamine regulation in different areas of the brain. What's more, a training study by Colzato, van den Wildenberg, & Hommel (2014) showed that genotypes linked to differential PFC dopamine transmission differed in their benefit from a flexibility game-training. Nonetheless, although this suggests that dopamine function seems to determine the degree to which transfer takes place after a training, this genetic relationship concerns prefrontal D1, rather than striatal D2. Knowledge on this topic is still scarce, and a direct connection with striatal D2 or EBR and individual training benefit has not been confirmed. Future research combining EBR measurement with genotyping and functional differences in executive control or benefit from cognitive training could clarify this relationship.

The primary purpose of this study was to investigate the relationship between striatal D2 dopamine and cognitive control functions in healthy elderly adults using EBR, focusing on individual difference among the older adults. We collected EBR before and after a longitudinal cognitive flexibility training (Buitenweg et al., 2017) assessed in a large group of healthy elderly adults. Based on previous literature we hypothesized that high EBR (indicating high striatal DA) should predict lower switching costs and increased SSRTs at baseline, but not baseline working-memory updating as measured with the Operation Span task. Considering the negative relationship with EBR found on an N-Back task (Zhang et al., 2015) we also studied whether the same result on this task would be found in older adults. Additionally, we wanted to know whether dopamine modulates training improvement and -benefit of a cognitive flexibility training in this population. We tested the hypothesis that the association between flexibility training and its benefits was different for varying levels of striatal dopamine availability. One possibility is that higher striatal dopamine availability is related to higher training success and transfer after flexibility training, but not after other interventions. Such a result would have meaningful implications for the state of cognitive training in aging, as it implies being able to predict which individuals profit more from this type of intervention. However, it is also possible that EBR is not sensitive enough to predict differences in training success, in which case other possibilities to investigate this relationship will have to be considered.

METHODS

This study is part of the overarching TAPASS training project (Buitenweg et al., 2017), a randomized controlled double-blind design intended to test effectiveness of a cognitive flexibility training.

Participants

Participants were healthy older adults (60-85 years old) interested in cognitive training. All participants owned a computer with internet, and scored 26 or above on the Telephone Interview Cognitive Status (TICS; Brandt et al., 1988). None used dopaminergic medication, or suffered from disorders associated with dopaminergic abnormalities (schizophrenia, Parkinson’s disease, ADHD), severe visual impairment or colorblindness or a history of substance abuse or stroke. The final sample included 158 participants, who were randomly assigned to one of three conditions (described below). Full written informed consent was given by all participants prior to participation. The study was approved by the local Ethics Committee of the University of Amsterdam and registered under number 2012-BC-2566. All procedures were conducted in compliance with the Declaration of Helsinki, relevant laws, and institutional guidelines.

Procedure

The study consisted of a pre-training (T0) and a post-training (T2) test session, approximately 13 weeks apart, with a 12-week training in between. During both sessions, a large testing battery was administered to assess transfer of this intervention, results of which are mentioned elsewhere (Buitenweg et al., 2017). Subjects were asked to sleep sufficiently and avoid alcohol the night before a test session. As EBR is found to be stable during the daytime hours, but increases in the evening (Barbato et al., 2000), testing was always done between 9 am and 6 pm.

At the start of the testing session, participants were asked for additional permission to make a recording of their face. They were not told the reason for the recording, so as not to draw conscious attention to eye blinks. Participants were seated about 80 cm distance from a white wall with a fixation cross (following Deuschl & Goddemeier (1998) and were asked to fixate on the target in a relaxed state without speaking or keeping their eyes closed. Although some suggest that 1 minute is enough to get reliable values of EBR (Deuschl & Goddemeier, 1998) most studies record for a period of 4 to 6 minutes (Colzato et al., 2009b; Slagter et al., 2015), which is followed in the current study. We recorded participants' faces for 5 minutes using a video camera (Canon Legria FS2000) that was visible to the participant, positioned at the height of their chin, approximately 60cm in front of them.

Intervention

We modified a selection of games from the existing website *www.braingymmer.com* to construct three training programs, based on our experience with cognitive tasks in older adult participants and our reading of the literature. The order of these games was pre-programmed to prevent participants from exclusively selecting the games of their choice. Each session consisted of approximately 30 minutes of game play.

Cognitive training

The cognitive training included nine games, divided over the cognitive domains working memory, reasoning, and attention. Two consecutive games were always from different domains, to increase variability and flexibility. Each game consisted of 20 difficulty levels. Feedback on game performance was given with zero to three stars on the screen after each game. Adaptiveness was maintained by encouraging participants to train at a higher level each time two or three stars had been attained. Within the cognitive training, we discerned two groups: frequent switching and infrequent switching. In the frequent switching condition, training sessions consisted of 10 games of 3 minutes each, forcing participants to constantly switch between different tasks and functions, thereby maximizing flexibility. In the infrequent switching condition, flexibility was minimized by allowing games in one session to be played for 10 minutes each. However, in the first training week, the infrequent switching schedule was enforced for both groups, to enable everyone to familiarize themselves equally with the games. After completion of the 12-week training, total time spent per game was the same for both groups.

Mock Training

The games in the mock training were selected to be predominantly visually stimulating. To reduce variability, fewer, less cognitively stimulating games were chosen compared to the experimental conditions. To minimize the demand on flexibility, games in one session were played for 10 minutes each. Although stars were attained in the same manner as in the cognitive training, we instructed participants to stay on a specific level for a week, thus reducing adaptiveness.

MATERIALS

Switch task

We used a switch task based on Rogers & Monsell (1995) which is known to measure most pure switching cost (van Holstein et al., 2011). In the switch task, stimuli were random combinations of a letter and a digit, appearing in one of four quadrants. Depending on which quadrant the stimulus appeared in, participants either responded to the digit or the letter. Digits were categorized as above or below 5, and letters as capitals or lowercase. To correct for possible eye movement effects, a horizontal and a vertical version of the task were created. In the horizontal version, stimuli in the top two quadrants required a response to the letter task, and in the lower two quadrants a response to the digit task. In the vertical version, a response to the letter task was required in the right quadrants, and to the digit task in the left quadrants. The task version was counterbalanced between participants, but was kept equal between time points within the same participant. The stimulus was presented in clockwise order, such that stimulus location on each trial was predictable, and a switch to the other task was required every other trial. Participants were encouraged to respond as fast and as accurately as possible. In between task blocks, participants were instructed to respond more accurately if accuracy fell below 91%, and to respond faster if accuracy rose above 97%, to maintain a balance between speed and accuracy. Presentation of the stimulus occurred for 5000ms, with an interstimulus interval (ISI) of 200 ms. Participants practiced the letter and the number task in separate blocks of 24 trials each. Subsequently, the switch task was practiced in a block of 32 trials. The actual task included four blocks of 48 trials. Switch cost was calculated by subtracting accuracy and reaction time on non-switch trials from switch trials, such that higher scores signified higher cognitive flexibility.

Stop-signal task

In the stop-signal task (Logan et al., 1984) participants are required to make a speeded response on Go trials and inhibit a response on Stop trials. In this case, participants indicated whether a green arrow, presented on the screen, pointed to the left or to the right (Go trial). In 20% of trials, the arrow turned red after a Stop Signal Delay (SSD), in which case participants had to withhold a response (Stop trial). To attain successful inhibition on 50% of Stop trials (Verbruggen & Logan, 2009), SSD before a Stop trial started at 300ms and was adjusted dynamically to individual performance, decreasing 50ms after a correctly inhibited response, and increasing 50ms after a failure to inhibit. On Go trials, participants were instructed to respond as fast as possible and not to wait in anticipation of a possible Stop cue. To ensure that our data did not include participants who waited on most Stop trials, we employed a cut-off of 10 to 90% correct inhibition and a minimum of 60% correct on Go trials (van Muijden et al., 2012). Stop-signal reaction time (SSRT) was calculated by sorting all correct Go-trial reaction times, taking the time corresponding to the percentage of correct stop trials, and subtracting the mean SSD from this number (Logan et al., 1984).

Operation Span task

For the Operation Span task (Unsworth et al., 2005) participants are asked to remember letters while simultaneously solving simple math problems. The Operation Span task therefore is thought to be a measure of updating or working memory. On each trial, single letters and equations were alternately presented on screen. Participants thus memorized a constantly updated string of letters, with a set size of 3 – 7 letters per trial. Following a complete set, participants were asked to recall the letters in the correct order by selecting them from a list on the screen. After entering the recalled string of letters, participants received feedback on performance on math operations and letter reproduction. There were 15 trials in total, with each set size presented 3 times in random order so participants could not predict how many items would be presented. Letters were randomly selected from a list (F, H, J, N, R, Y, K, L, Q, T, P or S). Regarding the math operations, participants were asked to evaluate an equation as being true or false (e.g. 4+4=7). Both tasks were first practiced separately. The letter practice task consisted of 4 trials of 2 to 3 letters, and the math task of 15 separate math operations. To prevent a trade-off between solving equations and remembering letters, an 85% accuracy on equations was required. The final score on the Operation Span task is the total number of correctly recalled letters.

N-Back task

In the N-Back task (de Vries & Geurts, 2014) a series of stimuli was presented, and participants were asked to indicate whether the stimulus shown is equal to the one presented *n* trials earlier. Stimuli consisted of black and white drawings of objects. Working memory demand was varied using three different difficulty levels: 0-back, 1-back and 2-back. The 0-back condition was used as a control, and required participants to respond with “yes” when a picture of a car was presented, and “no” for all other stimuli. In the 1-back condition participants responded with “yes” when the current picture matched the previous one and “no” if it did not. In the 2-back condition, participants responded with “yes” when the current picture was identical to the one shown two trials previously, and “no” if it was not. Participants were encouraged to respond as fast and as accurately as possible. The task was first explained on screen with oral instructions from the experimenter. Subsequently, participants practised all three levels of the task, using a paper-version practice block of 15 trials and an on-screen practice block of 24 trials. The experimental task consisted of four blocks of each level, with 24 trials per level. We implemented a minimum of 50% correct on the 2-back task, to prevent scores under chance level. Performance on this task was calculated as the difference between the percentage correct on 2-back and percentage correct on 0-back items (Kirchner, 1958).

Questionnaires

To assess fatigue, we used the Fatigue subscale of the Checklist Individual Strength (Vercoulen et al., 1997). Anxiety was measured using the Hospital Anxiety Depression Scale (HADS; Zigmond & Snaith, 1983). For more detailed descriptions of these scales, see (Buitenweg et al., 2018).

Training performance

We computed overall training Z-scores and gain scores between the first and last training session. To acquire Z-scores, we calculated the percentage of each level’s maximum possible score, and added up level scores to a total game score, and scores within each domain to a domain score. For each of the three conditions, we subsequently calculated the mean training score and transformed them to Z-scores.

Eye Blink Rate

The first 10 seconds of each recording were discarded, to prevent the instruction from interfering with EBR. The recording was viewed frame by frame across a 5 minute interval and scored for each blink by a researcher blind to the training condition. Movement of the eyelids was scored as a blink whenever the upper eyelid fully covered the pupil. EBR was defined as the mean number of blinks per minute.

Statistical analysis

We investigated the ability to use EBR as a predictor of cognitive control functions and training benefit in healthy elderly adults. For the first hypothesis, a series of linear regression analyses was carried out, with performance on Switch cost, Stop-signal reaction time, Operation Span task, and N-Back task as dependent variables, and EBR as the independent variable. A series of ANCOVAs were run for the second hypothesis, using difference scores for the N-Back task, SSRT and Switch cost, and training success (gain score and training Z-score) as dependent variables, Group as the independent variable, and Eye blink rate as the covariate. We included the interaction term Group * Eye blink rate to establish whether benefit of one training was higher for different levels of Eye blink rate. All participants who completed the post-training test session were included in the main analyses. Pearson's correlation coefficient was used for all correlations. Assumptions of normality and linearity were checked by inspecting the P-P plots and scatter plots of EBR with task scores. Homoscedasticity was checked by examining the scatterplots of the standardized residuals versus standardized predicted values. Correlations between all predictors were run to check for multicollinearity. Outliers were detected using Grubbs' Extreme Studentized Deviation test (Grubbs, 1950). We ran analyses with and without outliers. Reported results are without outliers. IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA) was used for all statistical analyses. A p-value of .05 (two-tailed if not mentioned otherwise) was considered significant. Bonferroni corrections for multiple testing were used for all analyses.

RESULTS

Participants

We invited 158 participants to the lab at T0, 107 of whom agreed to a short recording of their face. Participants who did not give permission for the recording were slightly older, $t(151) = 2.02$, $p = .046$, and more educated, $t(151) = 2.17$, $p = .032$, than those who did, but otherwise did not differ on baseline variables.

The video quality of two videos was too poor to calculate a reliable blink rate per minute. Two videos were too short, and one participant fell asleep while recording. One outlier was removed. Five participants were found to wear contact lenses, of which two participants wore only one. The difference in baseline EBR between participants with contacts (M=9.1, SD=4.1), and those without (M=15.2, SD=12.7) was not significant, $t(91) = 1.06$, $p = .29$. We therefore chose not to remove these participants from the sample. Data of 101 participants was used for analysis on T0 (age 60 − 85, $M = 67.4$, 61.4% female, mean years of education 13.4). Performance on all cognitive control tasks is shown in Table 1. After training, 38 participants agreed to a second EBR recording at T2. One participant did not follow the instructions, which rendered EBR of this person unusable. Thus, data of 37 participants was used for analysis of EBR post-training.

EBR results

Mean overall blink rate was 14.9 (SD=12.1) at baseline and 14.8 (SD=13.4) post-training. A high intercorrelation appeared between baseline and post-training measurements ($r= 0.86$, n= 37, $p<.0005$), and there was no effect of Time, signifying stability of this measure.

Blink rate was not correlated with gender or age. Although there was a tendency to lower blink rates in older adults between 76-85 compared to younger age groups, this was not significant. For this reason, blink rate was not residualised for age, as is done in Dreisbach et al. (2005) and Tharp and Pickering (2011). Figure 1 shows the mean blink rates per age category at baseline. Higher blink rate at baseline was associated with a lower reported state of fatigue ($r= -0.18$, n= 90, $p = .043$), and at post-training this relationship was even stronger ($r= -.41$, n= 36, $p = .006$). Blink rate was not correlated with reported anxiety. Results remained the same when including outliers.

EBR as a predictor of cognitive control performance

Simple linear regression analysis was used to test whether eye blink rate could be used to predict performance on Operation Span task, N-Back task, Switch task, and Stop task. For the Operation Span task, eye blink rate explained 10.7% of the variance ($R^2 = .107$, $F(1,69) = 8.30$, $p = .005$). Participants' predicted Operation Span task performance was equal to 56.01 - .34 * EBR. Although we expected no relationship, this suggests that increased EBR was related to a decrease in Operation Span. Additionally, eye blink rate was able to explain 8.7% of the variance of the N-Back task ($R^2 = .087$, $F(1,86) = 8.22$, $p = .005$). Participants' predicted N-Back performance equalled -8.71 - .17 * EBR, implying that increased EBR was related to a decrease on N-Back task performance, as

Table 1

Mean performance on cognitive control tasks

			M	s.d.
Switch task	Response time	Switch trials	1335.14	345.40
		Non-switch trials	976.32	327.66
		Switch cost	358.80	201.95
	Accuracy	Switch trials	92.03%	7.16
		Non-switch trials	94.33%	8.95
Stop-signal task	Response time	Stop-signal RT	263.83	55.50
	Accuracy	Stop trials	60.88%	13.75
N-Back task	Accuracy	N=0	95.34%	6.36
	Accuracy	N=2	85.17%	8.07
Operation Span task	Accuracy		69.46%	17.57

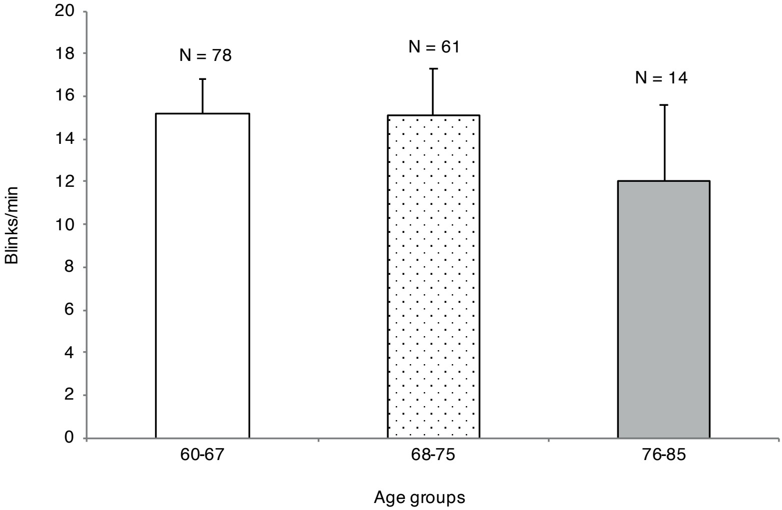

Figure 1. Baseline blink rate in three age categories in older adults. Error bars represent standard errors.

expected. For the switch task, a marginally significant equation was found. EBR explained 3.3% of the variance ($R^2 = .033$, $F(1,96) = 3.27$, $p = .07$). Participants' predicted switch cost was equal to -315.16 – 2.99 * EBR. In other words, counter to expectations, increased EBR was associated with marginally higher switch cost, though this was no more than a trend. Blink rate did not explain any variance of the stop task ($R^2 < .001$, $F(1,93) = .02$, $p = .88$).

As both significant results concerned accuracy measures, as opposed to latency, in order to determine whether measurement type played a role, we added an extra analysis of EBR predicting switch cost accuracy and stop-signal accuracy. Neither of these was able to be significantly predicted by EBR (both *p*'s > .17).

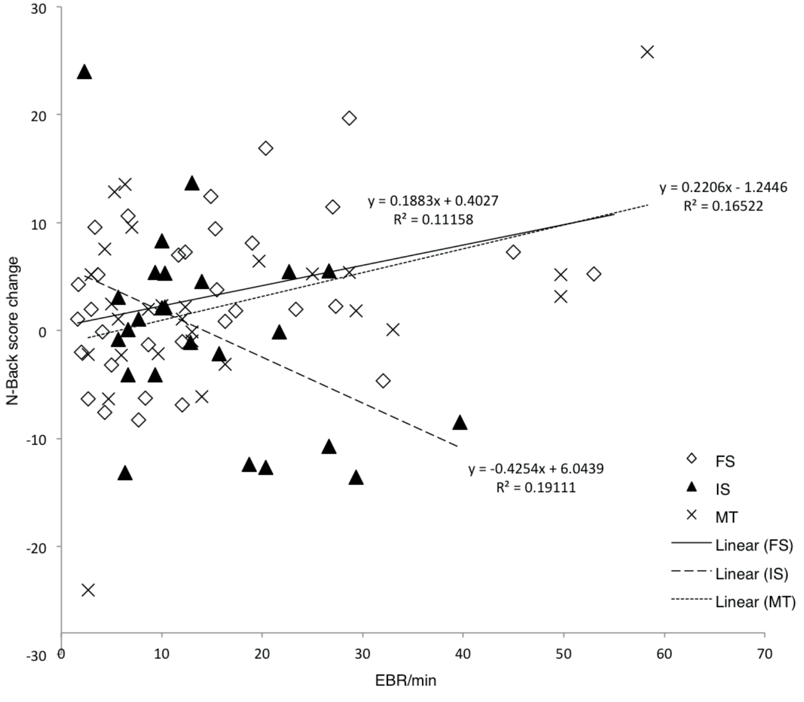

Figure 2. Interaction between eye blink rate and N-Back task score change over time for the different training conditions. FS= frequent switching condition; IS= infrequent switching condition; MT= mock training.

EBR as a predictor of training benefit

To test if EBR can predict training benefit, an ANCOVA was conducted between baseline EBR and difference scores on cognitive control tasks and training success, including the interaction between EBR and Group to determine if EBR affected benefit of one of the interventions. There was a significant interaction between Group and EBR on change in performance on the N-Back task, F(2,79)= 6.00, *p* = .004, η_p^2= .132. Plotting of this relationship revealed a negative regression line for the non-flexible intervention group compared to the other two interventions (see Figure 2). Eye blink rate was not related to a change in performance on the switch task, F(2,81)= .80, *p* = .45, the stop task, F(2,75)= .90, *p* = .41, or the Operation Span task, F(2,54)= 1.60, *p* = .21, after any specific intervention. Training improvement was not affected by an interaction between Group and Eye blink rate, both using gain scores, F(2,83)= .73, *p* = .49, and Z-scores, F(2,83)= .05, *p* = .96.

DISCUSSION

The present study used spontaneous eye blink rate to relate striatal dopamine to cognitive control functioning and trainability in older adults. Our results demonstrate that eye blink rate (EBR) significantly predicted performance on working memory updating, both as measured with an Operation Span task and an N-Back task. EBR failed to predict switching performance and response inhibition. Furthermore, EBR predicted training benefits on the N-Back task for two of the conditions, but not for any of the other tasks.

EBR as a predictor of cognitive control performance

Both N-Back- and Operation Span task scores were found to be negatively correlated to EBR. Although we expected no relationship with the Operation Span task based on the literature (Tharp & Pickering, 2011), the predicted correlation with N-Back task performance has previously been observed in young (Zhang et al., 2015). The latter suggests that it is possible to predict working memory function in older adults using an indirect measure of dopamine D2 availability. Our other hypotheses regarding a positive relationship with switch cost and a negative correlation with inhibition were not confirmed. This implies that despite previous findings in young adults—demonstrating prediction of these functions using EBR (Dreisbach et al., 2005; Colzato et al., 2009b; Kleinsorge & Scheil, 2017)—a similar relationship was not found in older adults.

There are several possible alternative interpretations for the present findings. One involves the differences in the tasks used in previous studies and the current one. For instance, in Tharp & Pickering (2011), the switch task consisted of only one switch per task block, whereas in ours a switch occurred every other trial. Also, their usage of the two *perseveration* and *learned irrelevance* conditions allowed participants with high EBR to respond to a novelty bias. As novelty was not present as an element in our own switch task, perseveration and distractibility were balanced. In Kleinsorge & Scheil (2017), the appearance of a pre-cue or a task cue allowed participants to prepare for a switch on certain trials but not on others, which introduced an extra element into the paradigm which was not present in ours. Accordingly, the tasks used in these studies differed from ours in such a way that they possibly tapped into different subfunctions.

Moreover, something that might have played a larger role in our sample of older adults than it did in the aforementioned samples of young participants concerns the speed-accuracy tradeoff. This phenomenon stems from participants' reluctance to make errors, thereby inadvertently choosing to spend more time on a task in order to keep the number of errors to a minimum (Starns & Ratcliff, 2010; Forstmann et al., 2011). This is observed in the very high percentage of correct stop trials, which should, by default, have stayed around 50% (Verbruggen & Logan, 2009), and does so in previous studies in young subjects. In our sample, despite removing the data of subjects with correct stop trials above 90%, the average percentage rose above 60%, suggesting that many participants waited in anticipation of the stop cue. We, therefore, cannot rule out that in our sample we were not able to measure inhibition in pure form, but in a form somewhat obfuscated by conservative response strategies.

Our working memory tasks covaried with EBR, while the switching and stopping tasks did not. A notable difference between those that did and did not covary is the focus on speed versus accuracy. Both N-Back- and Operation Span tasks emphasized accuracy, with less emphasis on speed, allowing participants to spend more time on each trial. On our switch- and stop tasks, by contrast, speed was central to performance, both by emphasizing the importance of speed from the beginning and by giving participants less time per trial, compared with said working memory tasks. Although we did not find any effects on the switch- and stop tasks in an additional analysis of accuracy, these measures are still embedded in a task that is greatly speed-related. One option for future research to attend to the speed-accuracy tradeoff is the use of a diffusion model, such as the EZ-model (Wagenmakers et al., 2007) to estimate currently unaddressed elements of participant behavior such as drift rate and non-decision time. Due to violated assumptions, this model was not applicable to our current data set. Nonetheless, we encourage the implementation of such models in further research to circumvent the tradeoff dilemma.

Besides the selection of similar tasks, one additional point to keep in mind when comparing studies that use EBR as a predictor of other functions, is that the average blink rate often differs from one article to the next, depending on the sample (Colzato et al., 2007; Colzato et al., 2009b). If the relationship is not linear, as is thought to be the case at least in the association with working memory and inhibition (Cools & D'Esposito, 2011) the results are greatly dependent on measurement of the left or right side of that curve.

Despite the many studies stating the possibilities of predicting performance on tasks relying on dopamine functioning with EBR, some recent publications find that these links pertain primarily to D1 (Colzato et al., 2009a; Colzato et al., 2014) whereas there does not seem to be a direct link between EBR and dopamine D2 receptor availability (Dang et al., 2017; Sescousse et al., 2018). While working memory function relies more on prefrontal D1 (Takahashi et al., 2008; McNab et al., 2009), stopping and switching has been tentatively related more to striatal D2 (Haluk & Floresco, 2009; Cools & D'Esposito, 2011), thus providing a suggestive explanation of why we found EBR to predict performance on working memory but not stop and switch tasks.

Although the average blink rate in our own sample was generally similar to that reported for older participants in previous literature (Deuschl & Goddemeier, 1998; Zaman et al., 1998), the variability was large, with some high and some almost absent blink rates. Though individual differences can be even higher in advanced age (Lindenberger et al., 2008; Mella et al., 2018), external circumstances might have played a role in this. For instance, stress or anxiety can increase blinks (Cruz et al., 2011). While in the current study anxiety scores were found not to be related to EBR, anxiety was assessed using an online, at-home questionnaire. It is possible that at the time of EBR measurement, a more temporary anxiety affected (i.e., increased) blink rate. Likewise, several participants reported that during EBR recording, while staring at the blank wall, they felt almost hypnotized, much like a meditative trance. Previous research demonstrates that long-time meditators show lower blink rates (Kruis et al., 2016), though this was not the case for short-time practice. As we did not register whether participants were long-time meditators or felt nervous or anxious during the test sessions, it is not clear whether the more extreme blink rates were caused by such circumstances or might just be ascribed to general individual differences.

EBR as a predictor of training benefit

Last, we observed that EBR is not predictive of training success in general or after a specific intervention, though the prediction of N-Back task improvement using EBR was found to vary for the different conditions. It is not entirely clear what might explain this occurrence, although it is likely that it is mostly driven by the negative predictive relationship between EBR and N-Back task on baseline. As the relationship between training improvement and activity and volume changes in the striatum have been found in young adults (Dahlin et al., 2008), it would be most relevant to investigate whether eye blink rate is able to predict training success at least in younger populations. Yet, as eye blink rate is an indirect assessment of dopamine activity, it is possible that the relationship between dopamine and training benefit cannot be demonstrated with this measure. Moreover, as the task improvements demonstrated by participants in our sample (Buitenweg et al., 2017) most likely occurred due to practice effects, another feasible explanation is that our training did not offer sufficient stimulation for benefit to take place and therefore did not support adequate prediction by individual elements. Further research should determine whether such an indirect relationship between eye blink rate and training benefit could be found.

In conclusion

To summarize, we determined prediction of working memory performance, but not switching or response inhibition, using EBR. EBR does not appear to be predictive of training benefits, at least not in the older adult population. The current findings suggest moderate possibilities in predicting working memory function in older adults using eye blink rate. Further research using the measurement of DA receptor availability along with EBR within this population is essential to determine whether this relationship can be demonstrated in older ages, providing us a necessary background for interpreting the link with cognitive control functions. Furthermore, investigations should focus on whether the currently found predictions hold also under different circumstances or with other tasks of working memory. Meanwhile, it remains essential to continue searching for a reliable predictor of functional cognitive decline, and possibilities for improvement, in the older population.

Chapter 6

Summary and general discussion

SUMMARY

Despite the neurocognitive deterioration that is generally associated with increased age, recent studies suggest that it is possible to stave off or slow down this decline and enhance mental functioning using cognitive training. The aim of this thesis was to determine whether frequent use of a cognitive flexibility training can be an effective way to maintain or enhance cognitive and subjective functioning in healthy older adults. In this final chapter, I will first summarize our most important findings regarding these questions. Following this, I will critically reflect on this study and on training studies in general, and discuss the implications and directions for future interventions.

At the outset of this project, a myriad of cognitive training studies was developing, promising far-reaching results, yet without being backed by guidelines on what makes up an effective intervention for older adults. We therefore reviewed the available training literature before 2012 to create an overview (**Chapter 2**) of the specific elements that show the greatest evidence of beneficial effects. We noted several methodological limitations in the current literature, such as the absence of control groups and short training times. Additionally, we argued that executive functions should be an essential ingredient of training, as they are crucial in guiding and monitoring performance in daily life and are susceptible to deterioration with increasing age. Promising avenues were discussed in training shifting, updating, and inhibition. We especially emphasized the addition of aspects of cognitive flexibility, particularly evident in task switching, given the enhancement of untrained functions (far transfer) demonstrated in the literature.

Additionally, a few relatively uninvestigated issues seemed particularly relevant to training in the aging population. First, including decision learning in training studies offers potential for improved outcome optimization, given the age-related behavioral differences and activation patterns in decision making and decision learning. Second, both integrating novel items into training sessions and creating interventions around novel skill learning were suggested to lead to benefits in functioning, by preparing the neuronal system for learning as well as develop new connections. Third, we advised an increased focus on training memory strategies, including considerable practice and individual choice, to investigate whether transfer of learning specific memory techniques might help older adults cope with situations on a daily basis. Fourth, the issue of individual variation in the population of older adults was raised, which can be addressed by creating adaptive training programs as well as identifying predictors of trainability.

We incorporated most of the above-mentioned aspects into our own intervention, the Training Project Amsterdam Seniors and Stroke (TAPASS), a randomized controlled trial, of which cognitive effects are detailed in **Chapter 3**. This study consisted of three programs, all including playing a combination of short computer games for 30 minutes a day for 12 weeks. Games for the first two interventions were diverse, cognitively stimulating, and adaptive. The third intervention, a mock training, was meant as an active control. Additionally, the first intervention required participants to switch between games of different domains (working memory, reasoning and attention) every three minutes, thus instigating and capitalizing on the need for flexibility. The second intervention required a switch every ten minutes, controlling for the elements of adaptibility and the diversity in games themselves. The mock training allowed participants to only play visually attractive games, demanding minimal cognitive stimulation and offering minimal adaptability. Cognitive effects were measured at four time points: before training, after 6 weeks of training, after 12 weeks of training, and 4 weeks post-training. Although most training gain was seen in the two interventions, all three conditions equally improved on measures of task switching, reasoning, planning, working memory, and psychomotor speed, all of which were further increased post-training. No benefit or disadvantage was found for individual characteristics. As we found no evidence for training-specific improvement, we interpreted these time-based increases as effects of motivation, expectancy and test familiarity, rather than an enhancement of underlying mechanisms of functioning due to specific elements of the training. Given these results, we further underscore the usage of both passive and active control groups in training research, as well as using parallel tests to limit retest effects.

Apart from the cognitive effects, we also examined how the training affected subjective mental functioning (**Chapter 4**). Effects were measured before and after training on subjective cognitive failures and executive dysfunctioning, everyday functioning, quality of life, depressive symptoms, and anxiety. Both subjective cognitive failures and executive dysfunctioning were also assessed 4 weeks post-training and were additionally rated by participants' proxies. No changes were seen immediately after training. Amelioration of subjective executive dysfunctioning and cognitive failures was seen at 4 weeks post-training, but with minimal effect sizes and equal improvement in all groups. Participants’ self-ratings for cognitive failures were significantly lower on both time points than those of their proxies, but proxies noted no changes over time. Several limitations notwithstanding, we concluded that computerized cognitive flexibility training was not advantageous for subjective mental functioning.

Individual variation within a group can lead to over- or underestimation of an intervention’s merit: a training might be especially advantageous for one, yet not for another. As striatal dopaminergic activity is strongly associated with age-related decline, we included spontaneous eye blink rate, an indirect measure of dopaminergic function, to predict executive functioning and trainability in older adults (**Chapter 5**). Eye blink rate was measured before and after training by requiring participants to focus on a fixation cross and recording their blinks for 5 minutes. Blink rate per minute was used to predict working memory updating, response inhibition and switching, as well as training improvement and transfer in the two interventions and the mock training. Eye blink rate significantly predicted performance of both measures of updating, but not of inhibition and switching. Eye blink rate also predicted transfer of the two interventions on one of the updating tasks, but not on any other tasks or on training gain. These results provide initial albeit modest hints at possibilities in predicting working memory performance using eye blink rate in older adults, although further research is warranted to thoroughly interpret this relationship.

Conclusion

To summarize, we concluded that our computerized cognitive flexibility training, based fully on the elements shown in previous research to be most effective, did not provide any further benefit to cognitive or subjective mental functioning in healthy elderly adults, beyond a non-flexible training or a mock training. Limited evidence could be found of individual differences predicting performance on cognitive tasks or on the training. Caution is advised in interpreting the (positive) conclusions of many earlier studies, given their methodological limitations.

GENERAL DISCUSSION

Our mission was to address the question whether it is possible to achieve beneficial effects using commercial training games with the elements of training that we suggested in Chapter 2 to hold this potential. However, we could not ascertain that including the elements of flexibility and variability is more advantageous for cognitive performance or subjective functioning than only playing a limited number of visually pleasing games for 12 weeks. It is quite possible that none of our interventions led to meaningful improvement, and that the increased performance on some tasks stemmed from practice effects. This explanation is backed up by Van de Ven (2017), who investigated effects of the same training in individuals who suffered a stroke, and Goghari & Lawlor-Savage (2017) who used the same website to train healthy older adults, both using a design that also included a passive control group. Results from these studies show that all groups, including the no-contact controls, improved equally on transfer tasks and subjective functioning (Goghari & Lawlor-Savage, 2017; Van de Ven et al., 2017a; van de Ven et al., 2017b). Similarly, a study comparing 12-week physical and mental training to a passive control group found equal amounts of transfer, using a composite score that included several tasks that showed time effects in our sample as well (Barnes et al., 2013).

In intervention studies, repeated assessment using the same tests is almost unavoidable. Yet, through familiarization with the test, or the use of strategies enabling faster or more accurate performance, retest effects are likely to occur. These effects are commonly larger in young than in older adults (Salthouse, 2009), though they are encountered in every possible age category. Indeed, in an estimation of practice effects on several neuropsychological tests, Salthouse (2009) confirms that many of them are susceptible to retest effects in older adults, even after a period of a year. As retest effects are frequently overlooked or underrated, this would lead to an overestimation of performance maintenance in longitudinal aging studies (Calamia et al., 2012). For this reason, the retest effect must be taken into account when designing future training studies, for instance by including a double baseline to eliminate most of this effect, or by statistically estimating the contribution of practice effects to an increase of scores over time.

Another interpretation of our results is that, given the increase in performance on our transfer tasks for all three conditions, brain training does work, but that any visually pleasing game will do, and the elements selected by us from previous literature are not critical in this respect. In this way, our active control was just as effective a training as the experimental conditions we had expected to show enhancement due to these features, even though our active control was designed to merely keep participants busy, controlling for the visual stimulation and the amount of time occupied performing the training games. Similar results are found by Wolinsky et al. (2016), reporting equal results from speed of processing training as from a control condition doing crossword puzzles; and by Grönholm-Nyman et al. (2017), finding equal improvement from shifting training condition and a control performing popular games such as Tetris. Similarly, perhaps actively committing to a 12-week program, creating the structured routine of completing a daily session, and having weekly calls with a member of the research team was enough to increase performance on certain cognitive domains, not to mention the time that was eventually spent by participants operating and getting more acquainted with their computers, during the training as well as outside it, developing general on- and offline skills.

We were careful to ensure that all groups received equal amounts of positive performance feedback during the training sessions and this may also have had a positive effect. Although it was our intention to keep the amount and nature of feedback balanced in all groups, positive feedback is associated with dopamine release and improved performance (Drueke et al., 2015; Harsay et al., 2010) and might have had this effect on participants in all conditions in the current study. Nevertheless, judging from the nonexistent changes in subjective functioning over the course of the training, any such changes were not explicitly perceived by participants, and therefore would have had to have been subconscious.

We expect that practice effects, or effects caused by expectancy, motivation, social interaction, positive attention and feedback, affect more training studies than is reported at the moment, given the fact that many do not include an active control given equal attention and social interaction, expectancy, and time on task. Indeed, if our experimental training regime had been more intense and our active control condition less active, differences between these groups might have been more pronounced. Yet, it would then be very difficult to pry apart the features of training leading to improved performance, which would defy the purpose of the active control. In this case, we can at least state that adding more variation in different cognitive domains within a session and imposing frequent shifts of attention to a different task, does not add more benefit to computerized brain training, contrary to what we had expected.

The role of individual differences

Our society consists of individuals from various backgrounds, each with different needs and abilities. In order to establish that a training does or does not work, we need to consider these individual differences and investigate in more detail for whom a training is or is not beneficial. In our case, we attempted to take inter-individual variation into consideration in a number of ways.

First of all, we examined whether individual aspects, such as age, level of education, baseline cognitive functioning, and the number of training sessions, were associated with training improvement or transfer. None of these were found to significantly explain individual differences in task performance or training benefits. Possibly, the variability on each of these variables was too low, due to our rather homogeneous sample, which we will reflect on further on. What is more, as the majority of the improvements seen in our study seems to be due to practice effects, it is reasonable to assume that the training was not challenging or stimulating enough to lead to additional benefit, thus not allowing for individual aspects to predict any differences in performance benefits.

Second, in testing the subjective effects of our training, it appeared that participants’ appraisal of their own memory functioning after training was associated more with subjective level of depression than with actual memory scores. Although not directly related to training, this finding does raise the issue that subjective evaluation of cognitive functioning is affected by other (e.g., emotional) individual variables.

Third, we tested whether eye blink rate, an indirect marker of striatal dopamine, is related to trainability and to the executive functions used as transfer measures. Although blink rate predicted working memory functioning at baseline, we did not find evidence of individual differences in dopamine functioning predicting general training effects, or benefits related specifically to flexibility training. Conceivably, there are a number of reasons for this. Previous research indicates that the striatum is actively involved in learning from training and that benefits from training can be predicted from individual variations in striatal activation (Dahlin et al., 2008; Erickson et al., 2010). However, eye blink rate is an indirect measure of dopamine activity and a relationship with learning or individual benefit from training has never been demonstrated, either in young or in older adults. Therefore, it is likely that eye blink rate is not a sufficiently valid measure of those aspects of dopamine functioning that may be related to training benefit. Furthermore, one other explanation is that the range of eye blinks expressed in our sample was too limited to be able to function as a predictor for the intricate construct of trainability. Of course, as we stated before, the training might not have offered sufficient stimulation for this neurobiological variable to be able to predict individual task performance.

Limitations of the current study

A number of limitations need to be taken into account. First of all, our participants were generally active, highly functioning and educated older adults. Some were still working or were engaged in regular volunteer work. The average age was relatively low: the few older adults above the age of 80 who initially displayed their interest in the study dropped out in the early stages. Similarly, individuals who showed more difficulty with the tasks, because of relatively impaired processing speed or (working) memory, reported that the extra effort required discouraged them from continuing with the training. Indeed, Van Deursen & Helsper (2015) note that especially lower educated and older individuals report to be uninterested in learning to use the internet, claiming to be “too old”. This provides an important confound that might explain why the subgroup that is underrepresented in the computerized training literature. As we did not pay participants or supply them with individual test scores or evaluation of their performance, those that chose to participate or remain in the sample did so either out of pure interest, to aid science, or because they believed it could help them in staying cognitively fit. By definition these individuals were already selecting their environment to accommodate them in their cognitive needs. In other words, our sample consisted, through self-selection, of older adults who were already conscious of or willing to contemplate about their health and fitness, and maintenance or improvement thereof. On the other hand, those who would actually be able to benefit from a training—presumably due to the age-related decline our training was meant to slow down—withdrew out of discouragement. Unfortunately, this is all too common in the training literature. In order to find answers to the questions surrounding training benefit in the population it is directed at, the self-selection bias is an issue that must be addressed.

Furthermore, one of the elements we meant to investigate in this study was unintentionally also present in the control group. Adaptiveness was intended to make up an important part of our interventions, as we expected that allowing individuals to train at their own pace would keep them feeling challenged, while at the same time experiencing sufficient amounts of success. However, many participants in the control group continued beyond the weekly level we set as a maximum, thereby compromising the limited degree of adaptiveness we had expected to incorporate in the active control training. For the current study, this means we cannot conclude that adaptiveness is *not* an effective element of training to enhance cognitive performance or subjective functioning.

Additionally, using the notion of task switching is unlikely to have been an effective method of inducing cognitive flexibility. Previous studies used task switching as a main component of training, generating transfer to untrained tasks (Karbach & Kray, 2009; Karbach et al., 2010). Others reported promising results from multitasking training (Bherer et al., 2005). We argued that by including task switching not as the domain of training, but as an element guiding participants' interaction with these games, we would expect enhanced flexible, adaptive thinking and strengthened novel neuronal pathways, demonstrated by improved performance on executive functioning. In retrospect, the complexity we had intended to achieve with this switching procedure likely was not sufficiently complex, and may even have led to confusion or irritability with our participants instead. Therefore, in order to precipitate transfer to relevant measures, we argue for a more in depth investigation of structurally complex interventions.

Recommendations

When conducting training studies, there are a number of basic factors we suggest to always include by default. First, active control groups should be used in order to control for equal attention, expectancy and all other training aspects other than that under investigation. Second, passive control groups and double baseline testing should be included in the protocol to control for practice effects. Third, we suggest that Bayesian statistics are used to test the likelihood of an alternative hypothesis (Dougherty et al., 2016; Guye & Von Bastian, 2017; Van de Ven et al., 2017a) because just using the p-value can over-rate effects of training and not supply any information about the strength of the evidence. Fourth, including measurements of individual factors that could be predictive of (individual) training success remains an important addition to training research. Besides these basic factors we also suggest a number of novel avenues for future training research.

Previous research has taught us that deterioration of executive functioning tasks is a good predictor of functioning in daily life (Owsley et al., 2002; Vaughan & Giovanello, 2010). Considering how we know these are related, it seems unfortunate that, as far as we know, no studies have investigated the exact link between executive functioning training and improvement on daily living activities. This is of utmost importance for brain training interventions, which routinely assume that training executive functions will improve functioning in daily life. What is more, very few studies do in fact find effects of training on daily-life functioning. Given the relationship between executive functions and daily activities, we might ask ourselves why training one does not improve the second. The most likely explanation seems that executive functioning training, in most cases, does not actually enhance the mechanisms of executive functioning in general but only very specific subfunctions that are less essential to the management of day-to-day activities. In this way, improvements shown on cognitive subtasks do not generalize to real world performance in daily life.

Brain training studies often address training of the brain from a perspective similar to that of physical exercise training. We all know that “if we don’t use it, we’ll lose it”: inactivity and disuse of our cognitive capacities will ultimately lead to loss of connections and slowing, and further disuse. The same principle applies vice versa: focused use of specific functions will be followed by strengthening of these regions and efficiency of pathways, demonstrated, for instance, in taxi drivers and professional dancers (Hüfner et al., 2011; Maguire et al., 2000). A common contention is that regular cognitive training regimes can lead to improved functioning, in the same way that physical training boosts muscle mass. However, this analogy holds only when training the same cognitive subfunction.

Brain training and its transfer effects are often seen in the light of creating an environment of task similarities instead of improving or strengthening the underlying mechanisms or allowing them to change neurological pathways. Indeed, if our general question in training research is, purely fundamentally, whether one can overlearn a number of basic tasks in such a way that one will improve performance on an untrained, yet nearly identical task, evidence affirming this has surely been demonstrated. Yet, rather than only regarding transfer on tasks that show similarities with the training and improving performance on those, a more pertinent question is whether fundamental cognitive processes are enhanced. Perhaps by letting go of standardized task-based training—often centered on one element, such as working memory—and by viewing cognitive training more as stimulating a broad spectrum of real-life behavior, it may bring us part of the solution to the problem it was meant to solve. A number of suggestions to stimulate this are elaborated on below.

In Chapter 2, we stressed the necessity for multimodal training, in such a way that participants need to stay alert and divide their attention over several stimuli. However, we now know that incorporating this idea into one fixed paradigm does not affect cognitive or subjective mental functioning more than control conditions. Perhaps we need to take a broader perspective on this. In order to bridge the gap between tasks used in training and the functions we actually want to see improved in daily life, one opportunity for future training in this population is to focus less on demarcated tasks and more on complex real-life learning, engagement, and skill acquisition. Previous studies have revealed that, for instance, learning to play an instrument or learning a different language can have lasting beneficial effects. Playing an instrument involves integration of cognitive, sensory, and motor functions, and lifelong music learning is found to be associated with increased gray and white matter and the absence of age-related reductions in volume (Bengtsson et al., 2005; Gaser & Schlaug, 2003; Wan & Schlaug, 2010). Likewise, as the use of an additional language requires continuous switching between different language systems, language learning is thought to lead to greater cognitive reserve and is associated with later onset of Alzheimer (Costa & Santesteban, 2004; Guzmán-Vélez & Tranel, 2015). Beyond skill learning and practicing, another opportunity which has proven to contribute in lowering the risk for age-related cognitive dysfunctioning is participation in volunteer work. Volunteering introduces one to novel activities, frequently combines physical, social and cognitive abilities, and can serve to fulfill a goal or purpose in contributing to society. An extensive review of the literature (Anderson et al., 2014) suggests that benefits are seen in physical and cognitive functioning, as well as quality of life and functional independence and daily life activities. More time devoted to volunteering is suggested to add to beneficial psychosocial effects (up to a maximum of about 2-3 hours a week) and benefits to positive affect and decreased depression symptoms are even more evident in individuals who are chronically ill or have sensory problems. A recent study in retired older adults found the risk for dementia to be decreased in those who participated continuously in voluntary work (Griep et al., 2017). Although separate physical, mental and social activities each have their own benefits on cognitive health, the integration of these efforts in volunteering is suggested to incur additional protective effects on cognitive health and longevity (Carlson et al., 2012; Karp et al., 2006) for instance through combined enhancement of cognitive reserve and vascular health (Fratiglioni et al., 2004). As such, combining multiple features is suggested to contribute more to generalized benefit than the separate elements would (Griep et al., 2017).

Granted, most of the above studies are cross-sectional and this raises the question whether social causation and selection could play a role in explaining the beneficial effects reported. Instead of the suggested relationship of skill learning and volunteering having a causal beneficial effect on health and functioning, it is likely that pre-existing differences, such as one's socioeconomic status, education, or health, partly underlie both cognitive maintenance and the individual choice to participate in said activities. For this reason, the use of random assignment and double-blind assessments are necessary in evaluating the objective merit of involvement in these activities. To illustrate, one randomized controlled trial demonstrated beneficial effects of instrument training on subjective well-being (Seinfeld et al., 2013), and a study by Balbag et al. (2014) in twins discordant for instrument learning showed that individuals that played an instrument during their lives have a lower risk for dementia compared to their musically uneducated co-twins. This strongly suggests that at the very least, pre-existing elements determined by genetics or upbringing do not account for the effect of instrument learning on the brain. Also, as growing up with a second or third language is not correlated with socio-economic status or education, beneficial effects of learning a language are not expected to be tied solely to individual choice possibly caused by pre-existing differences. In other words, there is at least moderate evidence pointing to causal effects of music and language learning on cognitive health. However, as most research into this matter does not involve random assignment, further research into the effects of skill learning and volunteer work is warranted, using randomized controlled trials and participants from diverse backgrounds.

Although we have pointed out specific opportunities for older adults to continue learning, an important prerequisite of learning in older adults is that activities should be catered to one's individual interests, spark curiosity

(Sakaki et al., 2018) and that benefits are regarded in ways that are individually relevant. Besides this, older learners need to be given the time to learn and to first master the most basic aspects of a skill before proceeding to levels that are more complex (Czaja & Sharit, 2016).

We have considered the issue of staving off or slowing down cognitive aging. Older adults who retire after approximately 40 years of work may expect to enjoy the rest of their life peacefully, without needing to perform on a daily basis, much like Johan at the beginning of Chapter 1. Yet, exactly this lack of stimulation can be highly detrimental to functioning in old age. As it stands, older adults do not fully use their potential, leading to a vicious cycle of further diminishing functions. In order for older adults to feel encouraged to learn, we feel that we need to involve, rather than alienate, older adults into society, not by (just) keeping them entertained but by keeping them challenged, and not by using straightforward, ready-made sessions but by integrating social, interactive, and creative, with cognitive and intellectual activities. This way, training should enhance abilities in the more general sense, subjective as well as objective, emotional as well as functional, measured in observable day-to-day living and subjective well-being at least as much as with cognitive laboratory tests.

Final thoughts

The prospect of enhancing cognitive control and other cognitive functions through brain training has important, widespread practical ramifications, both for older individuals, and for society as a whole. Older adults might live safely and independently for longer, without their loved ones fearing for their wellbeing. Years could be added to life, not only quantitatively, but also qualitatively, and in certain cases, the onset of dementia might even be postponed. However, we suggest computerized brain training is not in itself the way one should take to get there. We fully encourage older individuals to continue playing computerized brain games if they enjoy playing them, as long as they are aware that there is hardly any evidence that engaging in these games per se elicits any generalized benefit to executive functions, memory or other cognitive functions, or subjective mental functioning. For some, it might be discouraging to know that training in this manner is not as effective as it originally may have seemed. Yet at the same time, it opens up the possibility of discovering other activities that will contribute to cognitive health throughout the years.

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NEDERLANDSE SAMENVATTING

Hoewel toenemende leeftijd over het algemeen geassocieerd wordt met neurocognitieve achteruitgang, wordt in recente onderzoeken gesuggereerd dat deze achteruitgang kan worden vermeden of vertraagd, of het functioneren verbeterd, door middel van cognitieve training. Het doel van dit proefschrift was om te bepalen of regelmatig gebruik van een cognitieve flexibiliteitstraining een effectieve manier is om cognitief en subjectief functioneren in gezonde oudere mensen te behouden en te verbeteren.

Aan het begin van dit project was er een grootschalige ontwikkeling van cognitieve trainingsonderzoeken gaande. Hoewel deze ontwikkeling veelbelovend was, miste er een duidelijke richtlijn omtrent de cruciale trainingsaspecten van een effectieve interventie voor oudere mensen. Om deze reden hebben we een overzicht **(hoofdstuk 2)** gecreëerd van de beschikbare trainingsliteratuur tot 2012, waarin beoordeeld wordt welke specifieke trainingselementen het beste bewijs voor gunstige effecten laten zien. In dit overzicht wijzen we tevens op verschillende methodologische beperkingen in de literatuur, zoals afwezigheid van controlegroepen en te korte trainingen. Daarnaast voeren we aan dat executieve functies een essentiële component van training moeten zijn, gezien de cruciale rol in het sturen en bewaken van dagelijks functioneren en de gevoeligheid voor leeftijdsgebonden achteruitgang. We bespreken veelbelovende methodes voor het trainen van schakelvermogen, werkgeheugen en inhibitie, en leggen met name de nadruk op het toevoegen van aspecten van cognitieve flexibiliteit, die vooral duidelijk zijn bij het schakelen tussen taken, gezien de verbetering van ongetrainde functies (*far transfer*) die in de literatuur naar voren komt.

Daarnaast lijken een aantal relatief ononderzochte kwesties bijzonder relevant voor training in de vergrijzende populatie. Ten eerste biedt het opnemen van *decision learning* in trainingsonderzoek mogelijkheden voor het optimaliseren van resultaten, gezien de leeftijdsgerelateerde verschillen in gedrag en activatiepatronen bij het maken en leren van beslissingen. Ten tweede opperen wij dat zowel het integreren van nieuwe items binnen trainingssessies als het creëren van interventies rondom nieuwe vaardigheden kunnen leiden tot functieverbetering, door het neuronale systeem voor te bereiden op het leren en nieuwe verbindingen te stimuleren. Als derde adviseren we om meer aandacht te besteden aan het trainen van geheugenstrategieën, met voldoende oefening en eigen keuzes, om na te gaan of *transfer* na het leren van specifieke geheugenstrategieën oudere mensen kan helpen om te gaan met dagelijkse situaties waarin het geheugen een rol speelt. Als vierde stellen we de kwestie van individuele variatie aan de orde, die kan worden aangepakt door het maken van adaptieve trainingsprogramma’s en het identificeren van voorspellers van trainbaarheid.

De meeste van bovengenoemde aspecten zijn opgenomen in onze eigen interventie: het Trainingsproject Amsterdamse Senioren en Stroke (TAPASS), een gerandomiseerd onderzoek met controlegroep, waarvan de cognitieve effecten worden beschreven in **hoofdstuk 3**. Deze studie bestond uit drie programma’s, waarbij het spelen van korte computerspelletjes gedurende 30 minuten per dag, 12 weken lang, centraal stond. Spellen voor de eerste twee interventies waren divers, adaptief en cognitie-stimulerend. Het derde programma, een neptraining, was bedoeld als actieve controle. De eerste interventie vereiste dat deelnemers elke drie minuten schakelden tussen spellen van verschillende domeinen (werkgeheugen, redeneren en aandacht) waarmee cognitieve flexibiliteit werd gestimuleerd. De tweede interventie was bedoeld als controle voor de adaptibiliteit en diversiteit van de spellen, en verschilde slechts van de eerste door de vereiste elke 10 minuten tussen spellen te moeten schakelen. In de neptraining waren de spellen slechts visueel aantrekkelijk, en boden minimale cognitieve stimulatie en adaptibiliteit. Cognitieve effecten werden gemeten op vier tijdstippen: vóór de training, na 6 weken training, direct na de training en 4 weken na de training. Hoewel de meeste vooruitgang op de trainingsspellen binnen de twee interventies werd gevonden, verbeterden alle drie de condities evenveel op maten van schakelen, redeneren, plannen, werkgeheugen en psychomotorische snelheid. Verdere vooruitgang werd 4 weken na de training in alle condities gevonden. Individuele eigenschappen hadden geen aparte invloed op voordelen van training. Gezien we geen bewijs van trainingsspecifieke verbetering vonden, interpreteren we deze tijdsgebonden toenames als effecten van motivatie, verwachting en testbekendheid, en niet als verbetering van onderliggende functiemechanismen door specifieke trainingselementen. Met het oog op deze resultaten willen we het belang benadrukken van het gebruik van zowel passieve- als actieve controlegroepen en paralleltests om hertesteffecten in trainingsonderzoek te beperken.

Naast de cognitieve effecten hebben we ook de invloed van de training op het subjectief mentaal functioneren onderzocht (**hoofdstuk 4**). Effecten op subjectieve cognitieve fouten en executieve disfuncties, dagelijks functioneren, kwaliteit van leven, depressieve symptomen en angst werden voor- en na de training gemeten. Zowel subjectieve cognitieve fouten als executieve disfuncties werden tevens 4 weken na de training beoordeeld, en bovendien door proxy's van de deelnemers ingevuld. Direct na de training werden geen veranderingen gevonden. Op subjectieve cognitieve fouten en executieve disfuncties werd 4 weken na de training verbetering gerapporteerd, maar met minimale effectgroottes en zonder verschil tussen de groepen. Deelnemers' zelfbeoordelingen van cognitieve fouten waren op beide tijdstippen aanzienlijk lager dan die van hun proxy's, maar proxy's gaven geen indicatie van verandering over de tijd. Ondanks bepaalde onderzoeksbeperkingen concluderen we dat gecomputeriseerde cognitieve flexibiliteitstraining geen voordelen biedt voor subjectief mentaal functioneren.

Individuele variatie binnen een groep kan leiden tot een over- of onderschatting van de waarde van een interventie: zo zou een training voordelen kunnen bieden voor de één, maar niet voor de ander. Aangezien striatale dopaminerge activiteit sterk geassocieerd is met leeftijdsgerelateerde achteruitgang, hebben we spontane oogknipperfrequentie (EBR) gemeten, een indirecte maat voor dopaminerge functie, om executief functioneren en trainbaarheid bij oudere mensen te voorspellen (**hoofdstuk 5**). Knipperfrequentie werd voor- en na de training gedurende 5 minuten gemeten terwijl deelnemers naar een fixatiekruis keken. Met de frequentie per minuut werd getracht schakelvermogen, werkgeheugen en inhibitie, verbetering op de training, en *transfer* in de verschillende condities te voorspellen. Oogknipperfrequentie voorspelde prestatie van twee werkgeheugentaken, maar niet van schakelen en inhibitie. Oogknippers voorspelden ook *transfer* op een van de werkgeheugentaken, maar niet op andere taken of vooruitgang op de trainingstaken. Hoewel deze resultaten bescheiden mogelijkheden bieden voor het voorspellen van prestaties van het werkgeheugen in oudere mensen, is verder onderzoek noodzakelijk om deze relatie, en de associatie met dopamine, beter te kunnen interpreteren.

Conclusie

Samenvattend kunnen we concluderen dat onze gecomputeriseerde cognitieve flexibiliteitstraining, volledig gebaseerd op elementen die in eerder onderzoek als effectief werden bevonden, geen verder voordeel biedt voor cognitief of subjectief mentaal functioneren bij gezonde oudere volwassenen, vergeleken met een cognitieve training zonder flexibiliteit of een neptraining. Er is slechts beperkt bewijs gevonden voor het voorspellen van cognitieve testprestaties met individuele verschillen. Gezien de methodologische beperkingen van veel eerdere trainingsonderzoeken is voorzichtigheid geboden bij het interpreteren van hun (positieve) conclusies.

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