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Stockholm 2016

Plasticity of memory functioning: *Genetic predictors and brain changes*

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Karolinska Institutet

Published by Karolinska Institutet
Designed by Karin Bellander
Printed by Eprint AB 2016
ISBN 978-91-7676-499-2

Thesis for doctoral degree (Ph.D.)
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Plasticity of memory functioning: *Genetic predictors and brain changes*

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Abstract

Human cognitive functions are not determined from birth, but are plastic and can be altered by environmental factors. The promising idea of a cognitive intervention that would improve memory functioning has attracted a lot of attention over the last decades. By taxing memory functions through repeated training, researchers try to demonstrate improvement in the trained or other functions. However, people do not profit equally from these training regimes and their effect on brain integrity also differs between persons. In this thesis, I explore factors related to individual differences in cognitive training response, and their effects on the brain. The first part of the thesis concerns training of working memory (WM), and whether training-induced performance increases are influenced by certain genetic variations. The genetic variations studied are confined to genes related to the neurotransmitter dopamine (DA), which is related to cognitive performance. In Study I, we investigated the effect on WM training gains of single nucleotide polymorphisms (SNPs) in the LMX1A gene, previously linked to Parkinson's disease (PD). This gene is important for the development of DA neurons. For one of the SNPs, we found that over the course of four weeks of WM training, the two genotype groups showed a differential pattern of gain, such that those participants carrying the allele associated with a lower risk of PD showed larger gains. In Study II, we

examined if three DA related SNPs were associated with gain in several cognitive abilities, after 100 days of broad cognitive training taxing WM, episodic memory (EM), and perceptual speed (PS). The first one was the LMX1A SNP that was found to be linked to WM training gains in Study I. The second was a SNP in the DRD2 gene, important to striatal DA availability. The third was a commonly studied SNP in the COMT gene, coding for the enzyme that degrades DA cortically. We found that only the COMT SNP had an effect on training gains, and only for WM. The second part of this thesis focus on EM function, more precisely associative memory; if it could be trained, and what effects training may have on brain structure. In Study III, we explored process-based associative-memory training for older adults. Participants underwent six weeks of training on several different associative-memory tasks, with transfer tasks administered before and after training. An active control group underwent the same training, but practiced only on item memory tasks. No intervention effects were found for associative memory or the far transfer measures; however, the associative-memory training group showed larger gains than the controls on an item memory task. In Study IV, we used vocabulary learning as a way of studying associative-memory training. Participants studied a new language and their knowledge, effort, and cognitive capacity were measured. Before and after training, participants

underwent structural magnetic resonance imaging (MRI). We found that, compared to a control group, language learners showed increased grey matter (GM) volume in hippocampus. Furthermore, this volume increase was predicted by baseline capacity on a task measuring short term memory. Collectively, these studies show that the variability in training gains is not only noise, but rather meaningful variations that could be used to further our understanding of what factors determine the capacity for plastic change, both in brain and in behavior.

List of scientific papers

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

I Bellander, M., Brehmer, Y., Westerberg, H., Karlsson, S., Fürth, D., Bergman, O., Eriksson, E., & Bäckman, L. (2011). Preliminary evidence that allelic variation in the LMX1A gene influences training-related working memory improvement. *Neuropsychologia. 49*, 1938–1942.

II Bellander, M., Bäckman, L., Liu, T., Schjeide, B.-M. M., Bertram, L., Schmiedek, F., Lindenberger, U., & Lövdén, M. (2015). Lower baseline performance but greater plasticity of working memory for carriers of the val allele of the COMT val^{158}met polymorphism. *Neuropsychology, 29*, 247–254.

III Bellander, M., Eschen, A., Lövdén, M., Martin, M., Bäckman, L., & Brehmer, Y. (2016). *No evidence for improved associative memory performance following process-based training in older adults.* Manuscript submitted for publication.

IV Bellander, M., Berggren, R., Mårtensson, J., Brehmer, Y., Wenger, E., Li, T.-Q., Bodammer, N., Shing, Y.-L., Werkle-Bergner, M., & Lövdén, M. (2016). Behavioral correlates of growth in hippocampal grey matter structure during acquisition of a foreign vocabulary. *NeuroImage*, *131*, 205–213.

Contents

List of abbreviations

ADHD	Attention deficit hyperactivity disorder
COMT	Catechol-O-methyl transferase
DA	Dopamine
DMS	Delayed match-to-sample
DRD2	Dopamine receptor D2
EM	Episodic memory
GM	Grey matter
HC	Hippocampus
LCSM	Latent change score model
LMX1A	LIM homeobox transcription factor 1 alpha
MRI	Magnetic resonance imaging
PD	Parkinson's disease
PS	Perceptual speed
SNP	Single nucleotide polymorphism
WM	Working memory

1 Introduction

From infancy throughout childhood, the number and breadth of skills acquired are astonishing. This is made possible by a malleable brain, shaped by the interplay between genetic and environmental factors. The way in which the brain can be influenced by the environment, to change its organization and functioning, is interesting not only from a developmental perspective, but also because, if plastic changes routinely take place during the early stages of life, it is possible that these changes can be triggered later in life.

An intervention that could modify memory functions would have a huge impact if it is feasible when it comes to time and effort. For example, consider the memory decline in aging, sometimes leading to dementia. If memory functions could be improved, and this decline could be postponed by a few years, this would decrease the number of people suffering from these problems, hopefully increasing their independence and well-being. Or, think of general intelligence, a psychological construct that is highly predictive of educational and occupational success. If there are ways of influencing intelligence, the impact could be enormous. These visions motivate research into what is termed plasticity, and are key impetuses for the research pursued in this thesis. In the following, I will begin by giving an overview of the concept of plasticity and the way it is usually studied, before focusing specifically on the case of memory plasticity.

1.1 Plasticity

The term plasticity has witnessed an increased use within the field of psychology and cognitive neuroscience in recent years. It is not a new term, however; the first modern use of plasticity dates back to William James (1890), although its meaning has

changed considerably since then. When James wrote about plasticity, the basic architecture and functioning of the central nervous system were largely unknown. Since the introduction of the term, it has been further developed in the writings of, for example, Tanzi, Lugaro, Cajal, and Hebb (see Berlucchi and Buchtel, 2009, for a historical overview of the meaning of plasticity). Even though the use of the term has changed a lot since it was first introduced, it is still not used in a consistent way in the current literature. Rather, it has been taken to denote a wide range of changes in both brain and behavior.

When I use the term plasticity, I will for the most part follow the framework introduced by Lövdén et al. (2010). Here, the term plasticity denotes the capacity for change of the possible range of functioning. One key distinction in this framework is the distinction between plasticity and flexibility. Whereas flexible change reflects alterations between the functional states that the current system permits (functional supply), that is the possible range of functioning, plasticity reflects changes of this range. Flexibility is the fast response in the face of a change in environmental demands; plasticity is slower and triggered by a change in environmental demands during a longer period of time and an insufficient functional supply to match increasing demands.

A concrete example is the sudden reduction of functional supply by a brain trauma such as stroke. The trauma may force the system to adapt to the demands by first trying to flexibly solve various tasks in new ways, putting strain on the system which may now work at the limits of its reduced functional supply. After a longer period of time, plastic changes may start to appear, that is the functional supply increases and enables the system to solve the same tasks with less effort, and the loss of function caused by the trauma is reduced. Another example is trying to improve a cognitive function, such as working memory (WM), by training. The training may increase the functional demands, and the system would flexibly adapt to this increase. After a longer period of training, plastic changes may increase the functional supply, so that the capacity to retain information in WM is increased.

1.2 Cognitive training

Plasticity in cognitive functions is commonly studied empiri-

cally using training regimes, in which participants train one or many cognitive functions for a prolonged period of time. Performance increases attributed to plastic cognitive changes can be subdivided into two categories: changes in knowledge or representations and changes in processes. Changes in knowledge or representations can be to learn stimulus-response mappings, test-taking strategies, or content-related strategies. Changes in processes denote alterations in the mental process of interest (Lövdén et al., 2010). In the cognitive training literature, this is mirrored by the distinction between strategy-based and process-based training. Strategy-based training typically focuses on teaching strategies that may help in performing the task at hand, without affecting the ability per se. By contrast, process-based training targeting, for example, WM seeks to improve the actual ability, thereby affecting performance on tasks that depend on the ability in question. The distinction is illustrated by thinking of observed cognitive performance as determined by a multitude of factors, including basic abilities, motivation, test familiarity, test anxiety, and strategy use. This point is illustrated in Figure 1. Process-based training targets the abilities at the top of the figure, WM and episodic memory (EM).

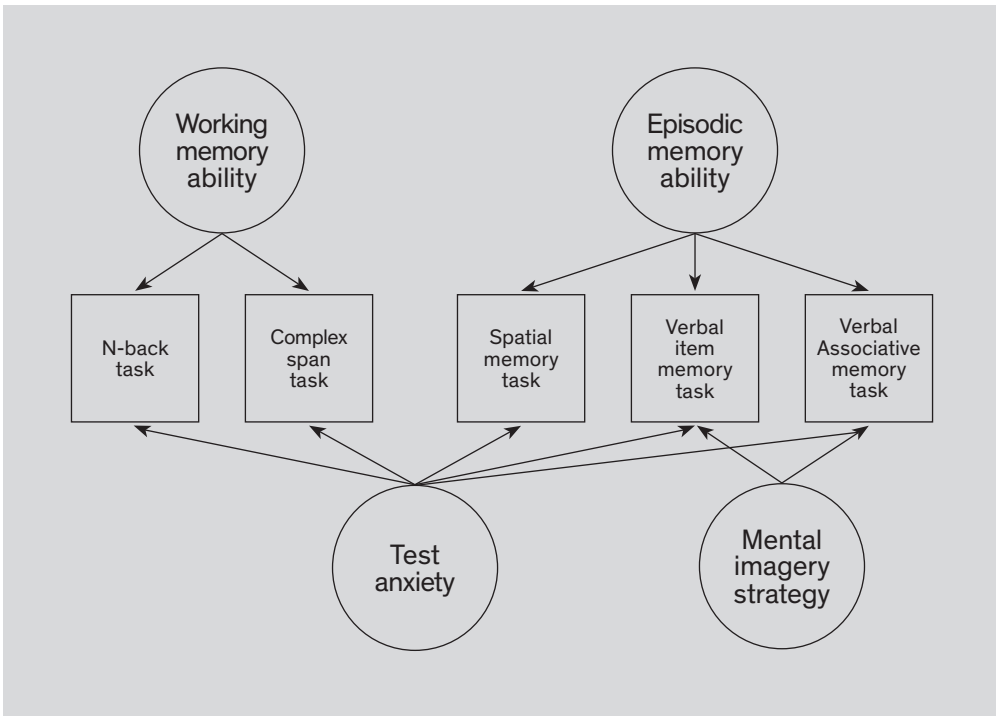


Figure 1. Schematic illustration of how cognitive performance could be determined. The boxes represent observed task performance and the circles denote latent factors that cannot be measured directly. The arrows represent the influence of a latent factor on cognitive performance.

Strategy-based training can add or improve strategies like that represented in the bottom right of the figure, mental imagery. In this example, the mental-imagery strategy only affects two of the three tasks included in the figure, illustrating that the use of strategies is often restricted to specific tasks and materials. It should be noted that, in practice, process-based training is never pure. Participants can develop strategies and acquire knowledge relevant to the task even if those are not given explicitly by the experimenter.

The studies in this thesis explore process-based training; therefore, I will focus on this type of training in the following, although I will give a short description of strategy-based training. Next, however, I will discuss how the effects of training can be measured.

1.2.1 Measuring the effects of training

When administering a cognitive training regimen, improvement on the trained task is almost always observed. However, it is impossible to determine what this improvement reflects without additional measures. This is so because performance is the product of multiple factors, such as cognitive ability, test familiarity, motivation, test anxiety, and strategy use, as illustrated in Figure 1. As the performance in itself does not permit conclusions about what caused the change, more intricate analyses need to be employed. Usually, a different task is administered before and after training, which is not part of the training but measures the same ability. The logic behind this is that if improvement is seen in a task that was not trained, the ability itself must have been altered. Depending on the specific ability targeted, it can sometimes be expected that other closely related abilities would also improve, that is training effects would transfer to these other abilities. Transfer tasks differ in their distance to the criterion task on a near to far transfer continuum. It has been suggested that the level on which the criterion and transfer tasks are related in the structure of human cognition should be the basis for the categorization of transfer distance (Noack, Lövdén, Schmiedek, & Lindenberger, 2009). This structure is hierarchically organized, with general intelligence at the top level. General intelligence is related to a number of broader abilities, and each broader ability is in turn related to a number of narrow abilities

(Carroll, 1993). Transfer within the same narrow ability would then be considered near, transfer between two narrow abilities belonging to the same broad ability can be termed intermediate, and transfer between two narrow abilities belonging to different broad abilities would be considered far transfer.

One problem with the common routine of only administering a different task measuring the same ability is that tasks can share some of the non-cognitive factors that affect the test scores (e.g., strategies, task familiarity, motivation). As a result, it is difficult to tell whether the tasks are correlated because they tap the same ability or because they are influenced by the same non-relevant factors. A way to resolve this dilemma is to use a latent-measurement approach. By using multiple tasks that measure the ability of interest and that differ in as many other dimensions as possible (e.g., modality, type of materials, set size, presentation rate), it is possible to construct a latent factor for the ability. This kind of model separates the task score variance into common variance for all tasks, which purportedly measures the desired ability, and task-specific variance, which captures all variance that is specific to a given task. The latent measure captures all variance that is common to the tasks used, and because measurement error is assumed to be task-specific, this latent factor is an error free measure of the ability. If an increase following training is demonstrated at the latent level, it is likely due to a true effect on the ability. This is so because it is unlikely that the diverse tasks used to construct the latent measure would be affected by the same non-task related knowledge and processes. This approach is rarely used in current cognitive training research, a major reason being that it requires relatively large sample sizes, which is often unfeasible, given constraints in time and money.

Note also that transfer tasks are not only administered to determine which abilities are improved or not, but also with the more pragmatic motive to investigate how general the effects of training are (for a taxonomy of transfer from this perspective, see S. M. Barnett & Ceci, 2002). For example, if it can be shown that WM training reduces everyday symptoms of attention deficit hyperactivity disorder (ADHD), which some authors claim (Klingberg et al., 2005; Klingberg, Forssberg, & Westerberg, 2002), this would be an important accomplishment even if the exact pattern of transfer remains poorly understood.

1.2.2 Strategy-based training

Strategy-based training aims at teaching participants a strategy that will help them performing various cognitive tasks. This approach has primarily been used regarding EM, and can focus on aiding both encoding and retrieval. Meta-analyses indicate that this type of training improves performance on the trained task (Gross et al., 2012; Verhaeghen, Marcoen, & Goossens, 1992). However, the effects of strategy-based training are limited to the specific task trained or to very similar ones (Jones et al., 2006; Stigsdotter Neely & Bäckman, 1995). This is likely so because strategies for specific tasks are usually inflexible and hard to apply to the wide range of situations in which new memories are formed. In addition, strategy-based training involves intentional encoding (which is required for strategy use). Therefore, it might not affect incidental encoding that is characteristic of everyday remembering (e.g., Kausler et al., 1986; Kausler and Wiley, 1991).

1.2.3 Process-based training

Process-based training, on the other hand, aims at improving the efficiency of basic cognitive processes, by administering repeated training without providing a strategy, and often by using tasks and materials that minimize the probability that participants use strategies spontaneously. This type of training has been used for improving various cognitive abilities such as WM (Klingberg et al., 2002), executive functions (Karbach & Kray, 2009), attention (Sohlberg & Mateer, 1987), and intelligence (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008). So far, the evidence for the effectiveness of these kinds of interventions is mixed. This thesis concerns process-based memory training, more specifically, WM and associative EM. I will continue by describing these two types of memory in relation to process-based training.

1.2.3.1 Working memory and working-memory training

To explore the extent to which cognitive functioning can be trained and how broad the effects are is not a new area of research (Kramer, Larish, & Strayer, 1995; Sohlberg & Mateer, 1987; Woodworth & Thorndike, 1901). However, the field was revived following some very promising results with computer-based WM training in the beginning of the new millennium (Klingberg et

al., 2005, 2002; Olesen, Westerberg, & Klingberg, 2004). These studies focus on training of WM, a function that holds limited amounts of information for short time periods while processing it and performing operations on it (Baddeley, 1992, 2000). WM is a fundamental part of our cognitive apparatus and is strongly related to fluid intelligence, the non-verbal and knowledge-independent ability to solve novel problems (Engle, Tuholski, Laughlin, & Conway, 1999). The reason for trying to improve WM was both because of its importance to cognition in general, but also because of a focus on children with ADHD, where WM deficits constitute a cardinal symptom. In these studies, both healthy young adults (Klingberg et al., 2002; Olesen et al., 2004) and children with ADHD (Klingberg et al., 2005, 2002) showed training-related WM improvements. Additionally, participants showed transfer to a measure of fluid intelligence and, for the children with ADHD, a reduction in symptoms of inattention and hyperactivity as rated by parents was observed (Klingberg et al., 2005). These results were seen as particularly impressive, because not only did they show that WM was malleable and could be improved by training, but training of WM also transferred to other abilities, such as fluid intelligence.

After the promising results of Klingberg and colleagues, a marked increase in the number of training studies followed. More recently, with the field reaching a critical mass, a few meta-analyses that focused on different aspects of the literature appeared. One of the early meta-analysis was performed by Melby-Lervåg and Hulme (2013). Having reviewed 23 studies with 30 group comparisons, the authors concluded that the WM gains were not maintained over time and did not generalize, thereby questioning the significance of these interventions. However, later meta-analyses found WM training to induce transfer both in older adults (Karbach and Verhaeghen, 2014; 49 studies with 61 comparisons) and in younger adults (Au et al., 2015; 20 studies with 24 comparisons). The results of these analyses were challenged by Melby-Lervåg and Hulme (2016), who re-analyzed the data, reaching the opposite conclusion. The data from Au et al. (2015) were also re-analyzed using a Bayesian approach, which showed strong evidence for a training effect when compared to passive control groups, but modest evidence for no effect of training when compared with active control groups (Dougherty,

Hamovitz, & Tidwell, 2016). This would suggest a Hawthorn effect, where learning to learn, task familiarity, and reduced test anxiety could explain the observed pattern. In response to this, Au et al. (2016) made the point that it is not the passive controls that underperformed in these studies. Rather, they performed better than the active controls; it is the training groups that are compared to passive controls that increase more. However, this argument is based on comparisons between studies, which is problematic, as other between-study factors that influence the training could correlate with design choices like type of control group. Melby-Lervåg, Redick and Hulme (2016) performed the most extensive meta-analysis so far, including 87 studies with 145 comparisons. In this analysis, they, again, concluded that the effects produced by WM training are limited to short-term improvements that do not generalize.

It should also be kept in mind that general conclusions using meta-analytic techniques are complicated by the heterogeneity in study designs. Studies differ on dimensions such as which abilities are trained, which type of tasks are used, the breadth of training, which transfer tasks are administered, length and intensity of training, whether a healthy sample or a clinical sample is trained, what kind of control condition is used, and the age of participants.

To conclude, the available meta-analyses have not been in agreement, and the debate between scholars is still ongoing. On balance, however, the evidence suggests that the initial beliefs about WM training resulting in widespread cognitive effects may have been overly optimistic. For example, even the optimistic meta-analysis by Au et al. (2015), where the type of control group was not considered, the net transfer effect, measured by the standardized mean difference, was 0.24, qualifying as a small effect size, according to Cohen's (1992) criterion.

1.2.3.2 Associative memory and associative-memory training

EM denotes long-term memory for events located in time and space (Tulving, 1983). EM can be subdivided into memory for single units of information (item memory) versus more complex binding of multiple units of information together (associative memory; Chalfonte & Johnson, 1996; Davachi, 2006). In every-

day life, memories are typically complex and require binding of several items together, or items and context. In EM research, item memory has received more attention than associative memory (Tulving, 2002). Longitudinal data indicate that, on average, EM is quite stable until around the mid-60s, when decline begins (Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). There are no such data for associative memory. However, when comparing item and associative memory using cross-sectional data, older adults perform much worse for associative memory than for item memory when compared to younger adults (Naveh-Benjamin, 2000; Old & Naveh-Benjamin, 2008; Schacter, Kaszniak, Kihlstrom, & Valdiserri, 1991; Yonelinas, 2002). Thus, it has been hypothesized that the difference between younger and older adults in EM largely reflects age-related deficits in binding information together (Naveh-Benjamin, 2000). In relating associative memory to the structure of the brain, volume of the hippocampus (HC) has been found to correlate with performance across age (Rodrigue & Raz, 2004). A magnetic-resonance imaging (MRI) study that subsegmented the HC found that larger grey matter (GM) volume of the CA3 and dentate gyrus (these could not be separated in the subsegmentation) were associated with better associative memory performance in older adults (Shing et al., 2011). In another study on older adults, grey-matter volume in frontal cortices was related to associative memory performance (Becker et al., 2015). The authors interpreted this result in terms of well-performing participants using effective strategies, thereby relying more heavily on frontal areas.

Associative-memory training is less studied than WM training. Traditionally, training of EM in general, and associative memory, in particular, has been strategy-based. There are very few process-based training studies that focus on associative memory; the increasing interest in process-based cognitive training has zeroed in on WM. There is, however, a tradition of studying how retention of information can be optimized by increasing the delays over which information has to be remembered (Schacter, Rich, & Stampp, 1985). This inspired Jennings and Jacoby (2003) to design a recollection-training regime for older adults in which participants had to remember word lists. In a subsequent recognition test the words were presented intermixed with new words. Importantly, the new words were

repeated so that, at the second appearance, participants had to remember the temporal context of the words in order to respond correctly. This training increased the delay over which participants could differentiate old words from the lures (Jennings & Jacoby, 2003; Jennings, Webster, Kleykamp, & Dagenbach, 2005), although transfer to other tasks has been negligible (Stamenova et al., 2014).

There are also studies that include associative-memory tasks in training batteries. One example is the COGITO study (Schmiedek, 2010). In this study, individuals trained for 100 days on multiple tasks tapping WM, EM, and perceptual speed (PS). Transfer on the latent level to near WM, EM and reasoning was found for younger adults, while older adults only showed WM near transfer. In the battery of trained tasks, there was at least one that had an associative component, and the same was true for the transfer battery used. In this specific associative EM transfer task, older adults showed a significant performance increase. Unfortunately, it is impossible to evaluate the effect of associative-memory training alone in this study, as the training was very broad.

1.2.4 Predictors of training gains

There is marked inter-individual variability in the size of gains from cognitive training. The inability of training studies to show consistent effects may partly stem from between-person differences in trainability, with some people not having much room for improvement, others improving quite a lot, and still others failing to utilize the training. As a result, the average net effect may be too small to detect with the usually small samples in cognitive training studies. There is a lot of potentially interesting information in this between-person variability that could hint at what factors are associated with greater plasticity. In this thesis, inter-individual variation in training-induced changes is investigated in Study I, II, and IV. In Study I and II, genetic information is used to predict cognitive training gains. Next, I will give a short description of some factors that have been studied in relation to the magnitude of training gains, and then discuss studies using genetic polymorphisms as predictors of the degree of improvement from training.

Predictors of gains have not been the center of attention in

training research, but a few different factors have been examined. One such factor is age, where the findings from studies that compare younger and older adults indicate that younger adults generally gain more from training than older adults (see von Bastian and Oberauer, 2014, for review). This pattern suggests that, although older adults have the potential to improve memory, the reserve capacity is still larger in younger adults (but see Karbach and Kray, 2009). Another factor is initial level of ability, and the question is whether cognitive training is mainly benefitting those who already perform at a high level before training (magnification), or if it rather is more helpful to those who are worse off (compensation). Extant research suggests that, for process-based working-memory training, compensation is the more likely outcome, whereas for strategy-based training, magnification is a more common pattern (von Bastian & Oberauer, 2014).

Genetic variations have been used in a few studies to account for differences in the ability to profit from cognitive training, because genetic factors are important for cognitive functions in general. Behavioral-genetic studies demonstrate that hereditary factors account for a substantial portion of the variance in cognitive performance. The genetic contribution is estimated to be 50% or more for WM (Ando, Ono, & Wright, 2001; Friedman et al., 2008; Wright et al., 2001), between 30% and 60% for EM (Papassotiropoulos & de Quervain, 2011), 40% to 80% for PS (Posthuma, Mulder, Boomsma, & de Geus, 2002), and 30% to 80% for intelligence (Deary, Johnson, & Houlihan, 2009). There are numerous candidate-gene studies relating specific polymorphisms to cognitive functions, and many of these involve dopamine (DA)-related genes (Savitz, Solms, & Ramesar, 2006). In the following, I describe the links between DA, cognition, and plasticity.

1.2.5 Dopamine, working memory, and plasticity

DA is a neurotransmitter that plays a key role in cognition. This has been shown in work on patients with severe DA alterations, experimental animal work, pharmacological studies, and research using molecular imaging techniques (Bäckman, Lindenberger, Li, & Nyberg, 2010; Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006; Cropley, Fujita, Innis, & Nathan, 2006). DA seems to be especially important to WM functioning, which

may reflect the fact that WM draws on a fronto-striatal circuitry, where DA plays an important role in controlling the signal-to-noise ratio in key neural networks (J. D. Cohen, Braver, & Brown, 2002).

Dahlin et al. (2008) reported that a letter-updating task activated the left caudate to a higher degree after five weeks of training than before training. The training also transferred to an untrained n-back task and, interestingly, an activation increase during n-back was found in the same region as for the trained task. No striatal activation increase was observed for a Stroop task that did not share any activation overlap with the trained task before training, demonstrating specificity of the effect. Thus, an overlap in neural activity between tasks may be one factor underlying transfer, and striatum seems to be important in mediating transfer of WM updating training. These results were further corroborated by Bäckman et al. (2011), where the same training regimen was used. In addition, positron emission tomography was employed before and after training to measure DA release. Compared to a control group, participants who trained WM updating showed greater increase in DA release after the intervention, in areas overlapping with those reported by Dahlin et al. (2008).

This link between WM training and DA activity gives further reason to study DA-associated genes in relation to WM plasticity. Indeed, several genetic variants have been found to influence gains from training of executive function (Colzato, van Muijden, Band, & Hommel, 2011), video game play (Colzato, van den Wildenberg, & Hommel, 2014), and WM (Brehmer et al., 2009; Söderqvist et al., 2012; Söderqvist, Matsson, Peyrard-Janvid, Kere, & Klingberg, 2014). Apart from a polymorphism in the brain-derived neurotropic factor, the polymorphisms in these studies were related to DA functioning.

As described above, WM training results in changes in brain function. I will end the introductory chapter by turning to EM interventions, and describe some of the associated structural brain changes.

1.2.6 Structural brain changes accompanying episodic memory changes

It has long been known that environmental changes can in-

fluence the structure of the brain in animals (Bennett, Krech, Diamond, & Rosenzweig, 1964; Rosenzweig, Krech, Bennett, & Zolman, 1962). This holds also for humans, as shown by research using MRI (Lövdén, Wenger, Mårtensson, Lindenberger, & Bäckman, 2013; May, 2011). The first study that showed experience-dependent increases in GM volume in humans using a within-subject design was performed by Draganski et al. (2004). In this study, participants practicing juggling for three months showed increased GM volume in areas relevant for the task (i.e., occipital-temporal regions). Since then, different types of cognitive interventions have also been found to influence brain structure.

GM increases in posterior parietal cortex and HC were seen after studying for a medical exam (Draganski et al., 2006). Mårtensson et al. (2012) compared military conscript interpreters learning a new language to matched medical student controls. They found GM increases after three months of intensive study among the interpreters in several areas important to language: left middle frontal gyrus, inferior frontal gyrus, superior temporal gyrus, and HC. The left superior temporal gyrus and right HC increases were related to language proficiency post training, whereas the left middle frontal gyrus increase was associated with how much they struggled during learning. Thus, both degree of learning and the effort expended were linked to GM increases. The HC changes found fit well with the fact that learning a new language involves the acquisition of a vocabulary, a process dependent on long-term memory, a function for which HC is integral. More specifically, the pairing of a word in the foreign language with its meaning may be viewed as an example of associative memory (Davis & Gaskell, 2009).

In the studies cited above, HC was one of the main areas showing plastic change. This sits well with the argument that the medial temporal lobe is the part of the brain that holds most promise for plastic changes, as the medial temporal lobe compared to other regions of the brain has a lower heritability and evolutionary expansion, and a higher variability in cortical thickness and higher myelin content (Walhovd et al., 2016). However, the spatial resolution of MRI is orders of magnitude from what would be needed to detect the neural underpinnings of the change. Thus, the specific causes of the observed macroscopic

changes remain unclear (e.g., angio-, synapto-, and neurogenesis, dendritic branching, and glia cell changes in numbers or size (see Zatorre, Fields, & Johansen-Berg, 2012, for review). The process of neurogenesis has been shown in specific areas such as the olfactory bulb, striatum (Ernst et al., 2014), and HC. In the dentate gyrus of HC, 1.75% of the neurons is replaced every year (Spalding et al., 2013). Wheel-running mice have been shown to increase their HC size more than their sedentary counterparts, and these changes are related to histological measures of neurogenesis (Biedermann et al., 2016). As alluded to, although neurogenesis might be one factor leading to GM changes in HC, there are additional factors that are likely to play an important role in these changes (Ho, Hooker, Sahay, Holt, & Roffman, 2013).

As with training-related behavioral changes, the brain changes that accompany cognitive interventions vary across persons. However, the sources of this variability are largely unknown. As mentioned, in the study by Mårtensson et al. (2012), brain changes were linked to language proficiency, but also to how much participants struggled during the intervention. This issue is examined further in Study III of this thesis.

2 Aims

The general goal of this thesis is to further the understanding of plasticity of memory functioning with a focus on individual differences therein. The thesis has two main foci. The first aim, pursued in Study I and II, is to investigate variations in DA-related genes in predicting performance gains following WM training. The second aim, explored in Study III and IV, is to investigate process-based associative-memory training, in terms of effects on behavior and brain structure, while examining predictors of potential brain changes.

3 Summary of the studies

3.1 Study I: Preliminary evidence that allelic variation in the LMX1A gene influences training-related working memory improvement

3.1.1 Background

LIM homeobox transcription factor 1 alpha (LMX1A) is a gene important for the proliferation, differentiation, and maintenance of dopaminergic neurons during the embryonic stage. Variations in this gene have previously been linked to early-onset Parkinson's disease (PD; Bergman et al., 2009), a disorder that is caused by death of dopaminergic neurons in substantia nigra. Bergman et al. hypothesized that one reason for the association between LMX1A polymorphisms and PD might be that individuals carrying disadvantageous alleles start off with less DA neurons from birth and therefore hit the threshold for PD earlier. As there is a relationship of DA to cognition and cognitive training, it would be of interest to test whether the LMX1A single nucleotide polymorphisms (SNPs) reported by Bergman et al. (2009) to be linked to PD are also associated with differences in cognitive performance and the ability to gain from WM training.

3.1.2 Participants

Twenty-nine healthy adults (18 women, 11 men) aged 20–31 years (M = 26.0) participated in the study. They were recruited via a newspaper advertisement and lived in the Stockholm area.

3.1.3 Materials and procedure

Participants were first tested on a battery of cognitive tasks tapping attention, EM, PS, and reasoning. Thereafter, they completed 20–25 sessions of computerized WM training at home over a

period of approximately four weeks. The training involved 7 tasks, 3 of which were verbal and 4 of which were visuospatial. The training was adaptive, so that difficulty increased as training progressed. An algorithm adjusted the difficulty level so that participants had about 60% of trials correct.

Participants were genotyped for three SNPs of the LMX1A gene: rs4657411, rs4657512, and rs6668493.

3.1.4 Statistical analyses

Because of uneven group sizes for the alleles of rs6668493, this SNP was dropped from further analysis. The genotype distribution for the rs4657411 SNP was 16 TT, 8 TC and 4 CC carriers, and for rs4657412 there were 18 TT, 8 TC, and 1 CC carriers. These were combined to form more balanced groups (rs4657411: 16 TT and 12 TC/CC carriers; rs4657412: 18 TT and 9 TC/CC carriers).

The training data were combined into a verbal and a visuospatial WM score for each session. These were then further aggregated to create weekly scores. The weekly scores were used in 2 (Genotype: TT, TC/CC) × 4 (Time: week 1–4) mixed ANOVAs.

3.1.5 Results

For both SNPs and both WM measures, a main effect of time was found, indicating that participants improved over time. There were no effects of genotype or a genotype × time interaction for either WM composite score for the rs4657411 SNP. However, for the rs4657412 SNP there was a significant main effect of genotype on the verbal WM score ($F(1, 25) = 5.13$, $p = .02$, $\eta_p^2 = .20$), such that TT carriers performed better that TC/CC group, and a trend in the same direction was observed for the visuospatial WM score ($F(1, 25) = 3.76$, $p = .06$). Critically, the genotype × time interaction was significant for the verbal WM score ($F(3, 75) = 3.99$, $p = .04$, $\eta_p^2 = .14$), reflecting that TT carriers improved more over time than the TC/CC group (See Figure 2). This effect was not significant for the visuospatial WM score ($F(3, 75) = 1.35$, $p = .27$).

3.1.6 Conclusion

These results demonstrate that the rs4657412 SNP had an effect on the ability to gain from WM training. However, this effect may reflect the training attenuating factors such as test familiarity and test anxiety. Consequently, a purer measure of WM may

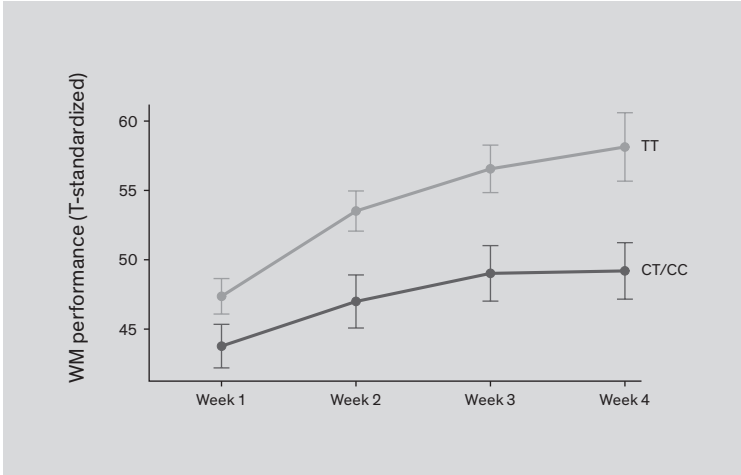


Figure 2. Verbal WM performance (T-standardized) across 4 weeks of training separate for the two genotype groups of the LMX1A SNP rs4657412. Error bars represent standard errors around the means.

have been obtained at the end of training, making the performance score more sensitive to detect genetic effects. Thus, the genotype groups may not necessarily improve differently; individual differences in WM may rather become more pronounced and measured more validly after training.

3.2 Study II: Lower baseline performance but greater plasticity of working memory for carriers of the val allele of the COMT val^{158}met polymorphism

3.2.1 Background

In this study, we investigated the effects of three different DA-related SNPs on the ability to gain from cognitive training. Rs4657412 in the LMX1A gene; rs6277 in the DA receptor D2 (DRD2) gene; and rs4680 in the catechol-O-methyl transferase (COMT) gene. The rs4657412 SNP was related to gains from WM training in Study I, and we sought to examine whether this finding would replicate in a larger sample. The rs6277 SNP has been shown to influence D2 receptor availability both striatally and cortically (Hirvonen et al., 2004, 2005, 2009). This SNP has also been linked to individual difference in cognitive performance (Bolton et al., 2010; Li et al., 2013; Papenberg et al., 2013). Rs4680 is a SNP in the gene coding for the COMT enzyme. This enzyme is involved in the degradation of DA, especially in frontal cortex. The variation in the COMT gene results in a met to val substitution. The met and val variants differ in the efficacy of the enzyme, with val homozygotes degrading DA about three times

faster than met homozygotes (Tunbridge, Harrison, & Weinberger, 2006). This functional difference has been related to behavioral differences between the genotypes. It has been shown that carriers of the met variant perform better in the Wisconsin Card Sorting Test (J. H. Barnett, Jones, Robbins, & Müller, 2007) and have slightly higher IQ, although there is typically no genotype difference in WM performance (J. H. Barnett, Scoriels, & Munafò, 2008). Interestingly, met carriers appear to perform better in tasks when maintenance of information in WM is required, whereas val carriers may have an advantage in updating tasks (Colzato, Waszak, Nieuwenhuis, Posthuma, & Hommel, 2010; Krugel, Biele, Mohr, Li, & Heekeren, 2009). This pattern of data might reflect the fact that the met allele confers an advantage in tonic DA activity, thought to be important for WM maintenance, whereas the val allele is advantageous for phasic DA activity, involved in WM updating. Given that WM tasks generally draw on both maintenance and updating operations, it should come as no surprise that met and val carriers often perform similarly in these tasks. This is so because the relative advantages of the alleles may cancel each other out.

3.2.2 Participants

There were 204 participants, 101 younger adults (20–31 years) and 103 older adults (65–80 years). The sample was derived from the COGITO study (see Schmiedek, 2010, for details).

3.2.3 Materials and procedures

Participants performed on average 101 daily sessions of cognitive training for about one hour each. They trained on 12 tasks from three cognitive domains: WM, EM, and PS. Before and after training, participants underwent extensive cognitive testing both on the trained tasks, but also on near and far transfer tasks measuring WM, EM, PS, and reasoning. For each ability, there were at least three different tasks with different contents (i.e., verbal, numerical, figural/spatial).

3.2.4 Statistical analyses

The reason for using multiple tasks with different contents was to allow for modeling the abilities in latent space using structural equation modeling. By constructing latent scores defined

by the common variance of the observed scores (indicators), a theoretically error-free measurement of the constructs of interest is obtained. There are models well suited for the analysis of longitudinal change in latent scores, such as the latent change score model (LCSM; McArdle & Nesselroade, 1994). We created LCSMs by forming latent measurements for the two time points (before and after training) using the task scores as indicators. A latent change score is specified by forcing the regression path from the first time point to the second, and from the change score to the second time point, to 1 (see Figure 3). Because the same ability is measured twice, it is important to make sure that the measurement of the latent construct does not change between the two time points. This is termed measurement invariance, and is a matter of degree (Meredith & Teresi, 2006).

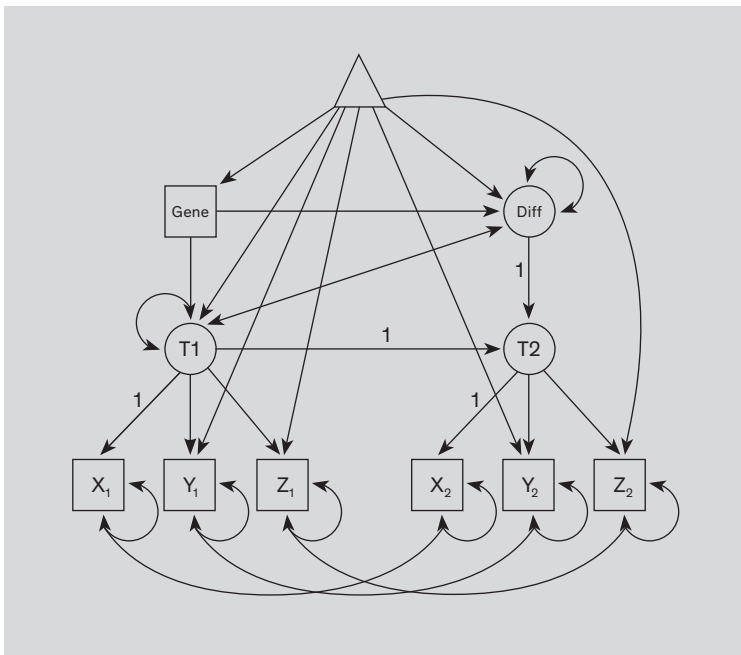


Figure 3. Schematic representation of the LCSM used in the analyses. Boxes represent observed variables, and circles represent latent variables. The triangle represents estimated means. Single-headed arrows represent regressions, and double-headed arrows represent variances and covariances.

Only latent variables for which strict or strong measurement invariance could be assumed were used in the analysis. These were WM-near transfer, WM-far transfer, PS-transfer, and reasoning. The genetic variables were added to the LCSMs as predictors of the change score and for performance before training. Each model had two parameters that were tested (the effect of the gene on change and on baseline performance), for the three genes and the four latent cognitive measures. This resulted in 24

significance tests. Due to the number of tests, the alpha level was set to 0.002, using Bonferroni correction.

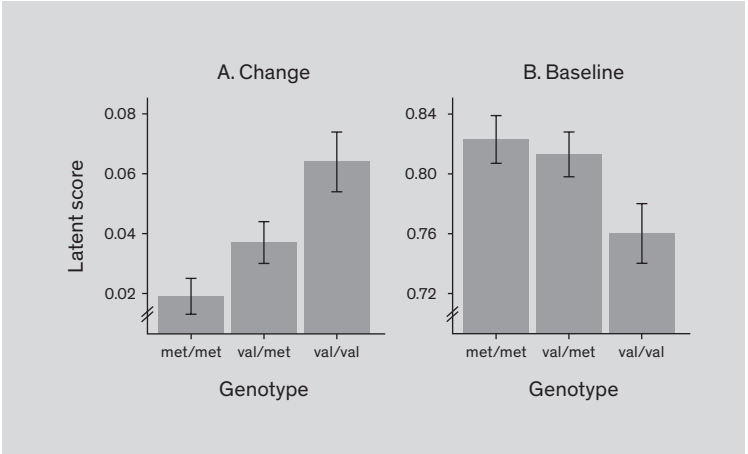


Figure 4. (A) Latent WM near transfer scores for change between baseline and post training, across the three genotype groups. Error bars represent standard errors. (B) Latent WM near transfer scores at baseline across the three genotype groups. Error bars represent standard errors.

3.2.5 Results

Neither the LMX1A nor the DRD2 polymorphism showed a significant effect on any of the cognitive abilities. However, there was a significant effect of the COMT polymorphism on change in WM-near transfer from before to after training ($\Delta\chi^2_1 = 14.19$, $p = .00017$), such that the gain from training increased with each val allele (Figure 4A). Although not approaching conventional significance after correcting for multiple comparison, the effect of COMT on the baseline scores for WM-near transfer were in the opposite direction, with met carriers starting off at a higher level than val carriers ($\Delta\chi^2_1 = 4.84$, $p = .028$; See Figure 4B).

3.2.6 Conclusion

Prior research indicates better performance of met carriers compared to val carriers on WM maintenance tasks, whereas the opposite pattern is often seen in WM updating tasks. A possible explanation of the current findings is that participants relied more on maintenance components when performing the tasks at baseline. During training, the updating component may have become more important, perhaps due to the latter component being more plastic, resulting in larger training gains among val carriers.

3.3 Study III: No evidence for improved associative memory performance following process-based training in older adults

3.3.1 Background

On average, EM starts declining in the 7th decade of life (Rönnlund et al., 2005; Schaie, 2005). EM can be divided into item memory, memory of individual items, and associative memory, the binding of items together (or items and context) into a coherent representation. Compared to younger adults, older adults' item memory is relatively intact, although their associative memory performance is much lower. There has been extensive research on the possible merits of computer-based training of cognitive abilities such as WM, executive functions, and attention, whereas studies of process-based training of associative memory is essentially lacking. The present study sought to remedy this scarcity by giving older adults training in associative memory and examining potential beneficial effects.

3.3.2 Participants

The study sample included 39 healthy older adults (M_{age} = 68.8 years) living in Zürich, Switzerland. Nineteen participants were randomized to an experimental group and 20 to an active control group.

3.3.3 Materials and procedure

Before training, participants were tested on measures of item and associative memory (near transfer), spatial memory (intermediate transfer), and reasoning (far transfer). Following baseline assessment, participants underwent 6 weeks of intervention. The same transfer tests as before training were given after the intervention. For both the experimental and the control group, the intervention was computer based. Each trial consisted of encoding, distraction, and retrieval. In the encoding phase, participants were shown object-word pairs that they were instructed to remember as pairs. This was followed by a distraction phase (arithmetic task) lasting for 30 sec to prevent influences from WM. These two phases were the same for the two groups. Finally, at retrieval, the experimental group was tested with associative cued recall, they were shown an object at a time and had to

type in the corresponding word that was paired with this object at encoding. By contrast, the control group was tested with item recognition; they were presented with an object or a word from the encoding phase or a new item and had to indicate whether they saw the same object/word at encoding. The number of pairs presented at encoding was constant for the control group (eight pairs). The training of the experimental group was adaptive, so that the number of items presented at encoding increased as training progressed, based on the individual performance.

3.3.4 Statistical analyses

The data were analyzed with 2 (group) × 2 (time) ANOVAs for each of the transfer measures.

3.3.5 Results

There were no significant effects whatsoever for associative memory (Fs < 1). For item memory, there was no significant effect of group ($F < 1$), but an effect of time ($F(1,37) = 6.10$, $p = .02$, $\eta_p^2 = 0.14$), and a time × group interaction ($F(1,37) = 4.49$, $p = .04$, $\eta_p^2 = 0.11$). This interaction reflected the fact that the experimental group improved more than the controls in item memory (Figure 5). For visuospatial memory and reasoning, only the effects of time were significant (visuospatial memory: $F(1,37) = 9.21$, $p < .01$, $\eta_p^2 = 0.20$, reasoning: $F(1,37) = 8.74$, $p < .01$, $\eta_p^2 = 0.19$).

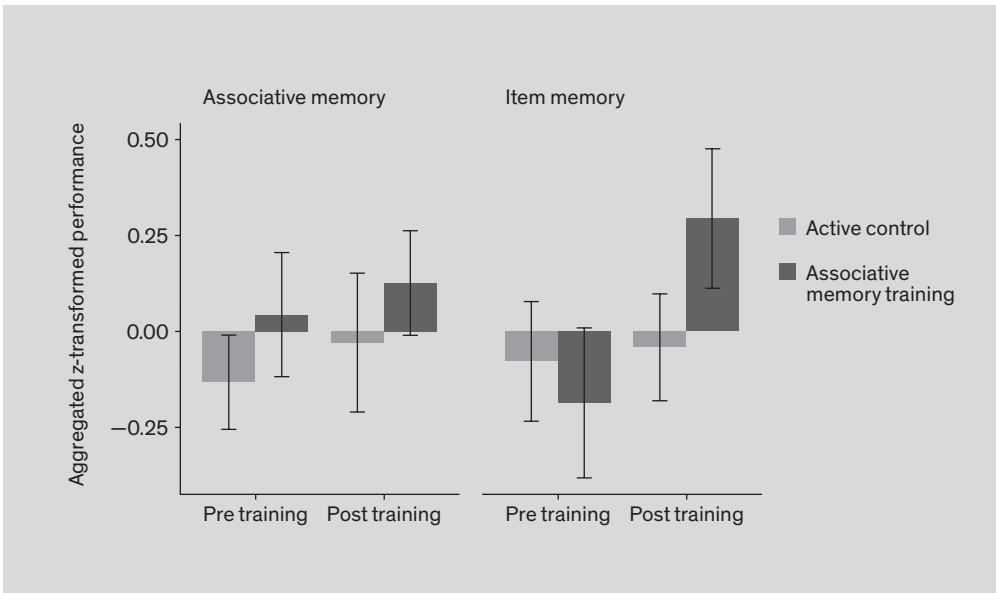


Figure 5. Aggregated z-transformed performance across the three associative memory tasks and across the three item memory tasks separately for the two experimental groups at pre- and post-training. Error bars represent standard errors around the means.

3.3.6 Conclusion

We failed to show that computerized adaptive associative-memory training improved performance on similar tasks more than non-adaptive item-memory training. However, there was a disproportionate improvement among those receiving associative-memory training in item memory. This finding might strike the reader as counterintuitive, as the control group underwent item-memory training. However, item memory is a prerequisite for associative memory, and training associative memory inevitably taxes item memory. Because the training of the experimental group was adaptive, their item memory might have been taxed more heavily than for the control group, thereby producing larger improvement in the experimental group.

3.4 Study IV: Behavioral correlates of growth in hippocampal grey matter structure during acquisition of a foreign vocabulary

3.4.1 Background

As noted, the occurrence of experience-dependent changes in brain structure in animals has long been known (Bennett et al., 1964; Rosenzweig et al., 1962). More recently, evidence suggests that this is true also for humans (Lövdén et al., 2013). For example, military interpreters learning a new language during a short period of time showed increases in hippocampal GM volume when compared to medical students (Mårtensson et al., 2012). Following the results of Mårtensson et al., we examined whether grey-matter changes would occur under more naturalistic circumstances, with a less select sample, and in a well-controlled experimental design. If so, we were interested in whether predictors of individual differences in these changes could be identified.

3.4.2 Participants

The sample consisted of 56 young adults between 18 and 30 years of age, who were recruited through an ad in a local newspaper. They were randomized into either an experimental group (n = 33), or a control group (n = 23). Participants were not allowed to have prior knowledge of any Romance language.

3.4.3 Materials and procedures

The experimental group received Italian language training, focusing on vocabulary acquisition, as a way of studying associative memory in a natural setting. In addition to participating in an Italian class once a week, they learnt new words using an iOS application developed for the study. The data from this application were downloaded, which enabled us to extract the number of words they learnt, as well as how much time they spent studying with the app. The control group went to weekly meetings where they watched Italian movies with Swedish subtitles, which was assumed not to affect their Italian vocabulary. Before and after the intervention, participants were tested on a cognitive battery including an associative-memory task and a delayed match-to-sample (DMS) task. They also underwent MRI to obtain T_1-weighted images. After the intervention, the experimental group performed a test to determine their Italian vocabulary.

3.4.4 Statistical analyses

The MRI data were analyzed with SPM8. A paired t-test for time was performed in the experimental group, to detect potential changes that could be used in the predictive model. A follow-up whole-brain group × time mixed analysis was performed to make sure that potential time-related group differences were specific to the experimental group. GM values from the clusters indicated in the primary analysis were then extracted and analyzed in path models to determine whether training-related characteristics or baseline cognitive measures were associated with GM changes.

3.4.5 Results

The whole-brain analysis for the experimental group showed reliable increases in two separate clusters, one in the right HC and one in the left occipital lobe. In the group × time analysis, only the hippocampal cluster was significant, confirming that the change in this area was specific for the training group. The average GM probability in the right HC cluster was used in path models to investigate predictors of GM change. In the first model, time spent studying and vocabulary size after training were used as predictors of GM change, and time spent training were also used as a predictor of vocabulary size (see Figure 6A). This

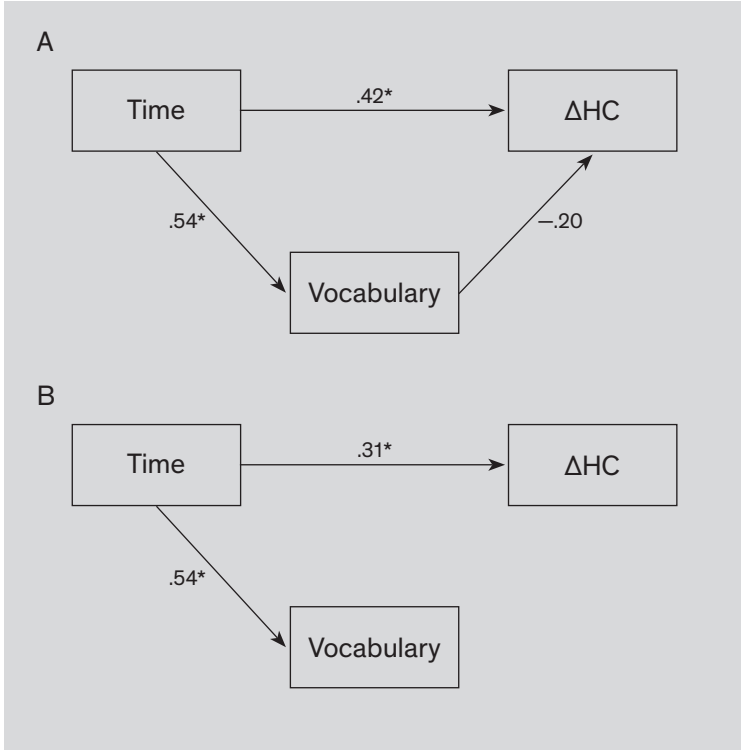


Figure 6. The basic path model of the relationship between time spent studying, vocabulary test score, and GM change in the right HC, (A) full model, and (B) pruned model.

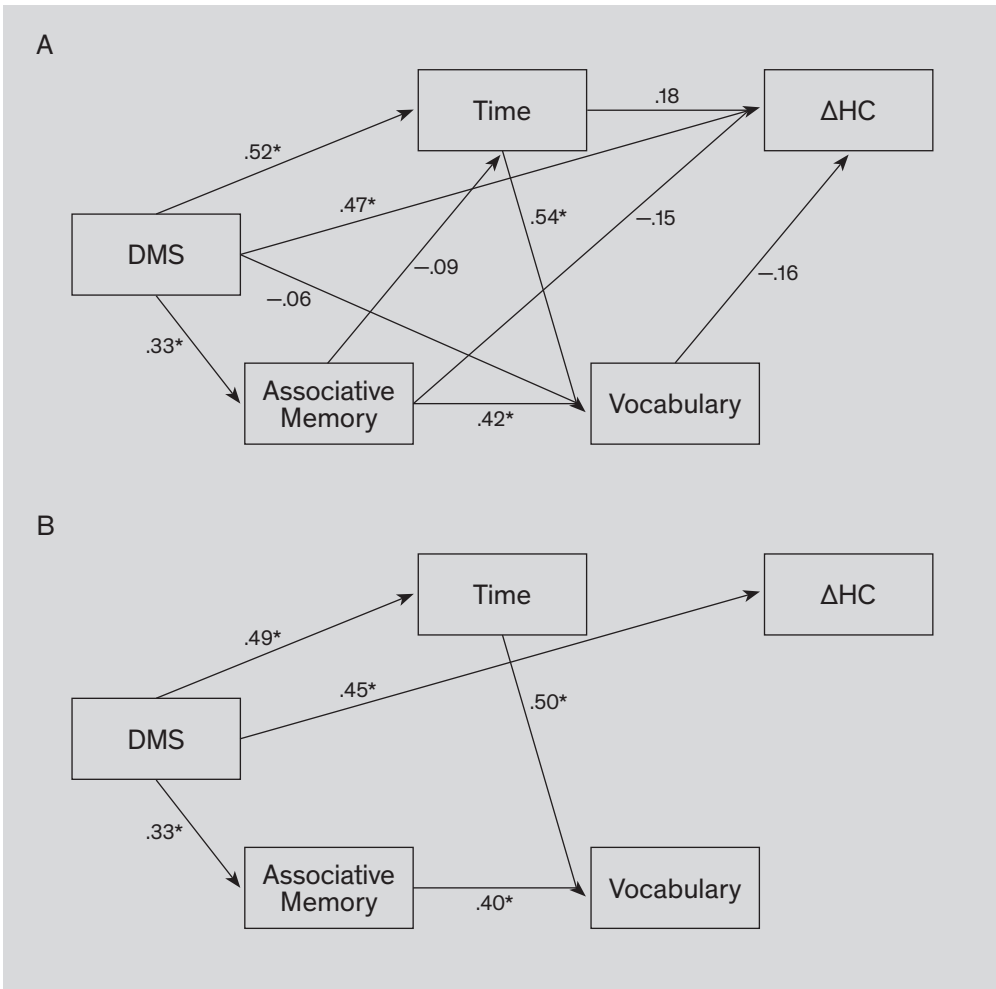
model showed that time spent studying predicted both vocabulary acquisition and GM change (Figure 6B). In a second, more complex, model, we also added performance on the baseline DMS and associative-memory tests. We let the DMS and associative memory scores predict all three variables in the simpler model. In addition, we added DMS as a predictor of associative memory, as DMS may measure a low-level ability on which associative memory in part could depend. (Figure 7A). When adding these baseline measures, the original pattern changed; in the new model, DMS predicted associative memory, GM change, and also time spent studying. In addition, time spent studying and associative memory predicted vocabulary size. (Figure 7B).

3.4.6 Conclusion

The changes in GM probability observed in this study are in line with the results from Mårtensson et al. (2012). We also show that the time spent studying seems more important for the observed GM changes than the amount of Italian vocabulary acquired. That is, brain changes related to associative EM training might be more a function of use of the ability than of the degree of in-

crease in vocabulary. However, when adding baseline performance to the model, only performance on a DMS task predicted HC change. This task holds similarities to pattern separation tasks, which have been related to neurogenesis in the human HC. This opens up for the possibility that the volumetric changes observed could be partly due to neurogenesis, although other sources (e.g., angiogenesis, synaptogenesis, dendritic branching, and astrocyte increases) are possible.

Figure 7. The extended path model where baseline performance of associative memory and delayed match-to-sample is added, (A) full model, and (B) pruned model.



4 Discussion

4.1 Summary of the results

In this thesis, I present results from four studies all investigating human memory plasticity. In two of the studies (Study I and Study II), effects of DA-relevant genetic variations on the ability to profit from WM training were examined. In Study I, WM performance at the end of the intervention was related to a variation in the LMX1A gene. In Study II, a variation in the COMT gene was found to influence the gain in WM following the intervention. The other pair of studies (Study III and Study IV) focus on process-based EM training. First, we explored the effects of a computerized associative-memory training regimen in older adults (Study III) and then we examined changes in GM measures using MRI following the acquisition of a new vocabulary in young adults, as a way of studying associative memory (Study IV). Although Study III failed to show transfer to non-trained associative memory measures, an increase in item memory performance was found. Study IV found GM increases in HC after the acquisition of a new vocabulary, and these GM changes were related to baseline cognitive ability.

4.2 The promise and challenge of genetics in cognitive training studies

The purpose and possible gains of studying genetics in relation to memory training might not be entirely clear. How could these results be used? I think that research investigating genetic effects on cognitive training benefits is best understood as a basic-science project aiming at better understanding cognition and how it is implemented in the brain. Take the case of Study II, where the COMT SNP, of which we know the biological effects, was found to influence WM trainability; thus, this genetic

information could be seen as a surrogate of information about differences in people's brains. In other words, instead of experimentally intervening in participants' brains, we can use the genetic information as an indicator of between-person differences. Although this non-invasive technique may provide information about participants' DA systems, it is admittedly crude and does not permit true experimental inferences.

Moreover, Study II also generated a hypothesis that could potentially be tested, namely that the updating component of WM is more malleable than the maintenance component. This is something that future research could potentially investigate, thereby increasing the understanding of plasticity of cognitive functions. This is a prediction that might not have been derived in other ways. A secondary, more distant, result is that finding single genes, or genetic profiles, that affect plasticity or the sort of training you gain from could be used to decide what type of training a person should receive, or be informative as to whether training has the potential to be effective at all. This perspective is much in the same spirit as personalized medicine (Schork, 2015).

Low power is a recurrent problem in psychological research in general, and might be even greater in cognitive training research due to practical reasons. First, the effects, if any, are small using current training methods. It would be foolish to think that a total of a few hours of training would radically alter stable cognitive functions formed under thousands of years of evolution. Second, sample sizes are typically small. Training research is also time consuming and costly, as participants are tested at multiple occasions and required to undergo sessions of regular training over a certain period of time. In cognitive training studies using genetics this is further complicated, as the effects of common genetic variations on cognitive performance is typically small (Payton, 2009), and there is no reason to assume that the corresponding effects on change in cognitive performance should be much different.

A different perspective on cognitive training was taken in Study I. Here, we viewed the training also as a way of increasing the validity of the cognitive measures, by attenuating the influence of other variables that may affect cognitive performance and individual differences therein, such as test familiarity, test anxiety, motivation, strategy use, and task-relevant knowledge

(Baltes & Kliegl, 1992; Kliegl, Smith, & Baltes, 1989, Figure 1 illustrates that test scores are influenced by multiple variables). This may make it easier to disclose genetic effects on cognitive performance after training, because persons are closer to their maximum performance level. The obvious downside of this approach is that training studies are time-consuming and costly, and it is debatable whether the gain in precision is worth the cost in time and money.

4.3 Can cognition be improved by training?

First, the answer to the question in the above heading obviously depends on how you define "improved by training". Even though the evidence is scarce for generalized training effects of the interventions used in current research, this does not mean that better regimens cannot be developed. To be sure, cognitive functioning is determined by multiple environmental factors, and is therefore often under our control. This thesis focuses on interventions aimed to improve cognitive performance. I have not discussed non-cognitive training approaches, which might affect cognitive functioning. A non-cognitive intervention with strong positive evidence is physical exercise. Apart from its physical benefits, positive effects on cognitive functioning are routinely observed following exercise interventions, even though these effects too are generally small (Colcombe & Kramer, 2003; Roig, Nordbrandt, Geertsen, & Nielsen, 2013; Smith et al., 2010). Another intervention that has been explored, although with little supportive evidence, is transcranial direct current stimulation (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016; Horvath, Forte, & Carter, 2015). But if we focus on the cognitive side, think, for example, of formal schooling: An extra year of schooling has clear effects on fluid intelligence (Lager, Seblova, Falkstedt, & Lövdén, 2016). Furthermore, consider the Flynn effect, the fact that each new generation perform better than the one before on tests of intelligence (Flynn, 1987) and other cognitive abilities (Rönnlund & Nilsson, 2008), which is something that is difficult to account for by genetic selection. One (out of several) proposed explanations for the Flynn effect is secular changes in educational attainment (Blair, Gamson, Thorne, & Baker, 2005).

Thus, cognition is not a fixed entity, although it might take

quite some time and effort to change it. If we accept the critique of cognitive training studies, and think that the evidence for improvement is weak, might not better training procedures be devised? It is probably naive to think that interventions lasting for a few weeks should result in large and generalizable gains; perhaps more intense and longer interventions are required. However, this idea is not supported by the meta-analysis of Melby-Lervåg et al. (2016), where moderator analysis generally found no effects of training dose on transfer effects. Note, however, that the authors dichotomized the dosage variable into either low dose (less than 10 hours of training) or high dose (more than 10 hours), which makes this analysis less informative. That said, the results of Melby-Lervåg et al. are supported by findings from the meta-analysis of Au et al. (2015), where neither session length nor number of sessions had any clear effects. The latter study treated these variables as continuous and yet their influence was negligible. The weak relationship between dosage of training and the size of the effect is worrisome for cognitive training research, as you would think (and hope) that these variables should be related.

Second, the question as to whether WM (and other cognitive functions) can be improved also depends on how you define the term improvement. It is dependent not only on the data used by different researchers. Even when analyzing the same data, investigators may arrive at different conclusions (Au et al., 2015, 2016; Dougherty et al., 2016; J. Karbach & Verhaeghen, 2014; Melby-Lervåg & Hulme, 2016). The two sides in the debate on the existence of transfer effects take different approaches to the subject. In general, those claiming that there is no transfer of WM training put a stronger emphasis on theory, whereas those who take a more positive stand are more data-driven. A more pragmatically minded and data-driven researcher might assign a higher probability to cognition being trainable, because even though the data might not fit with current theories of cognition, the data are still there and can be viewed as demonstrating that cognition can be improved. For example, the fact that transfer effects are mostly observed in comparison to passive control groups (rather than active controls) allows for the possibility that the performance increase seen is due to improvement in factors affecting test performance that are not part of the training, such

as test familiarity and motivation. If the exact reasons for an observed performance increase are not the focus of interest, this can be taken as an indication of transfer. The same is true for the weak relation between criterion task improvement and magnitude of transfer (Melby-Lervag et al., 2016), which is problematic from a theoretical point of view. For researchers with strong adherence to a theoretical model of cognition or specific parts of cognition, such data will conflict with their theories, and they might not want to grant the performance changes the grace of being called transfer. To conclude, the disagreement between these groups of researchers depends to a large extent on their theoretical investment in the WM construct and their views on control groups.

4.4 Why at all improve cognition?

As discussed, research about how to improve cognition can be important in its own right from a basic-science perspective. It can help understanding cognitive functions and how they are implemented in the brain. However, are there other reasons, more linked to everyday life? Are there any practical insights to be made from these studies? Let us put aside the controversies about whether training actually works, and assume that we find a way to reliably improve people's memory, or other cognitive functions. What has to be the case for this to be interesting in a translational sense? I think that there are many conditions that need to be satisfied for this type of training to have translational relevance.

First, the cognitive function needs to be improved to a large enough extent. The effectiveness of a particular method might very well be proven, but the effect on the ability also needs to be large enough to be of interest. Second, the intervention should not take too much time. There has to be a balance between the time you invest and the potential gains. If the training has reasonably sized effects, but requires a large amount of time, it might not be worth the effort. Third, the effects have to show some generalizability. It should not be task specific, and preferably transfer to other similar domains (this is of course not necessary for training to be useful, but all things being equal, broader effects are preferable). Fourth, the training has to be ecologically relevant. That is, there have to be real-life effects on

memory or other functions dependent on memory (or whatever ability is targeted) in natural settings. If the effect is seen only in laboratory tasks, and there is no change in people's everyday functioning, there is little use of the training from an ecological point of view. Fifth, better cognitive functioning in real life has to come with something positive (e.g., regarding well-being and life satisfaction). It is not obvious that people need better memory to function in everyday life, at least not the aspect of memory that may be improved following traditional training programs. For example, training benefits should translate into educational achievements in children and younger adults, better job performance in adults, or increased independence and quality of life in older adults. And, as alluded to, if all these requirements are met, and the casual pathway exists, the effect at the end of the chain needs to be large enough in relation to the effort put into the training to begin with. Thus, for a training paradigm to be interesting with regard to everyday cognitive functioning, there are lots of hurdles to pass.

4.5 Structural brain changes related to learning

Study IV showed GM increases in HC, which might reflect plastic changes. To draw conclusions about the nature of these changes, knowledge about how they develop over time would be needed. At this point we do not know if the changes are transient or long lasting. In a study where right handed participants learnt to write with their left hand and underwent MRI several times during this process, a pattern of expansion in relevant brain areas, followed by partial renormalization, was observed (Wenger et al., 2016). If such a pattern is true for the changes in HC reported in Study IV, it could indicate the learning and integration of a new skill.

Structural changes were observed in response to learning a new vocabulary, and these changes were more strongly related to the time spent studying than the actual size of the acquired vocabulary. This could be interpreted as these changes representing a reorganization in response to the training so that new memories could be stored more efficiently. However, if this were to be the case, transfer effects would be expected to other EM measures, but Study IV failed to show transfer to an associative-memory task, which was arguably similar in several ways to learning a new vocabulary.

4.6 Future directions

I think that inter-individual differences in plasticity and predictors of plasticity is an important avenue for future research, given the goal of finding ways to reliably improve specific aspects of cognitive ability. Regarding the empirical results in this thesis, I think that one interesting prediction from Study II is based on the finding that COMT val carriers had a more plastic WM than met carriers, and it was hypothesized that this may reflect a val advantage in the updating component. This could be tested by training individuals separately on maintenance and updating, and examine whether it indeed is the case that val carriers profit more from updating training than met carriers, who rather might show greater plasticity in the maintenance component.

Study III failed to show an effect of associative-memory training in older adults. This could be because of a flawed design of the training regime, or because associative memory is not easily trainable in aging. However, given the large differences in associative memory performance between younger and older adults, testing this type of training in younger adults to see if it works, could be a possible way to go. If a training effect can be demonstrated in younger adults, with better associative memory, and a more plastic brain, then maybe this regime can be adapted in a way to also benefit older adults. Building on the findings in Study IV, it would be of interest to further investigate the nature of the GM changes observed. First, we might use different MRI techniques, such as diffusion tensor imaging, to probe the underlying cause of the volumetric changes. Second, behavioral measures specifically tapping pattern separation would be useful, to examine if such measures improve the prediction of GM change. As Study IV only recruited younger adults, it would also be of interest to investigate whether this language learning-dependent GM plasticity extends into old age and, if so, whether the same factors account for inter-individual differences in GM change in aging.

A general recommendation for future studies is to use larger sample sizes than current studies. Training effects are probably small, and sufficiently large sample sizes are needed to detect them. For obvious reasons, this is even more important when studying inter-individual differences in the magnitude of gains.

To also boost the potential effect of the training to meaningful levels, new training regimes also need to be more intense and longer lasting than the current ones. Another methodological problem in the current literature that needs to be considered in future studies is the way in which transfer is measured. Transfer to untrained tasks should not be equated with plastic changes in the process under study. Plastic changes could lead to limited transfer if the process improved is one that is not important for a broad number of abilities. Reversely, broad transfer can be seen even when no plastic changes occur in the trained ability, for example through decreased test anxiety following training (see Figure 1). To measure change in the cognitive process of interest, latent measurements based on thoughtfully chosen tasks should be used. The tasks should be selected so that they all tap the process of interest, but reduce all other possible factors that could be shared in determining the test scores. Latent measurement was used in Study II of this thesis, but was not used in the other studies.

The time may now be ripe for more large-scale intervention studies, dissecting the mechanisms of training so that more effective regimes can be developed. Here, the individual-difference perspective is again important, as it might not only be the case that there is an optimal design for cognitive training, but the optimal design might vary between groups and individuals, depending on genetic profile, chronological age, and baseline cognitive ability, among other factors. Even though I think it is too early to give up the hope for interventions that can alter cognitive functions, I think it is important to be open to the possibility that plasticity of adult cognition is smaller than perhaps previously thought.

5 Acknowledgements

If you've read this far, you're definitely among the ones who deserve a thank you. Stort tack till mina tre handledare Lars, Martin och Yvonne. Lars för din skärpa och tydlighet. Martin för din pragmatism och latenta variabler. Frau Dr. Brehmer för din entusiasm, din struktur och dina balkongmöbler. Also, many thanks to all the members of the psychology group (both past and present) for many fruitful discussions, helpful comments, and a friendly work environment. Det finns många som har förgyllt min tid på KI. Ylva, Nina och Lieke, ni är så fina, jag kommer sakna er. Jag vet att vi har åtminstone ett oavslutat projekt som jag hoppas vi slutför. Mina förebilder Björn och Armita, jag hoppas jag får jobba med er igen. Dr Oetker och Lillan som inspirerade och underhöll mig under psykologprogrammet. Lars och Rasmus, som fick mig att börja studera psykologi från första början, och som förstår allt jag säger, typ innan jag sagt det. Tanaz, Ida, Andreas, och resten av Emotion lab, tack för en sådan välkomnande, och inspirerande stämning. Tack Julia för givande diskssioner och fester. Marion, för nya perspektiv och större frågor. Sigrid, Lisa, Isak, och Robban, ni är det roligaste, smartaste och snyggaste MR-sällskapet jag kan tänka mig. Trots eventuella brister denna avhandling innehåller så är den åtminstone det utan tvekan snyggaste som någonsin tryckts på Karolinska Institutet, tack Karin! Lotte och Bengt, tack för att ni tog tillvara på min nyfikenhet och lät mig få utlopp för den. Tack alla mina vänner för den delen av avhandlingen som jag inte skrev.

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