

Train your Brain

Updating, Transfer, and Neural Changes

Erika Dahlin



Department of Integrative Medical Biology
Section for Physiology
Umeå University, Sweden
2009

© Erika Dahlin 2009
Umeå University Medical Dissertations
New Series No. 1283
ISSN 0346-6612
ISBN 978-91-7264-834-0
Printed at Print & Media, Umeå University

Abstract

Dahlin, E. (2009). Train Your Brain - Updating, Transfer, and Neural Changes. **Doctoral dissertation from the Department of Integrative Medical Biology, section for Physiology, Umeå University, S-901 87 Umeå, Sweden.** ISBN: 978-91-7264-834-0

An initial aim of this thesis was to determine whether training of a specific executive function (updating) produces improvements in performance on trained and transfer tasks, and whether the effects are maintained over time. Neural systems underlying training and transfer effects were also investigated and one question considered is whether transfer depends on general or specific neural overlap between training and transfer tasks. An additional aim was to identify how individual differences in executive functioning are mapped to functional brain changes. In Study I, significant training-related changes in performance on the letter memory criterion task were found in both young and older adults after 5 weeks of updating training. Transfer to a 3-back test of updating was also demonstrated in the young adults. Functional Magnetic Resonance Imaging (fMRI) revealed overlapping activity in letter memory and 3-back tasks in fronto-parietal areas and striatum pre-training, and a joint training-related activity increase for the tasks in a striatal region. No transfer was observed to a task (Stroop) that engaged fronto-parietal areas, but not the striatal region and updating per se. Moreover, age-related striatal changes imposed constraints on transfer. In Study II, additional transfer tasks and a test of long-term maintenance were included. Results revealed that training-related gains in performance were maintained 18 months post-training in both young and older adults, whereas transfer effects were limited to tasks requiring updating and restricted to young participants. In Study III, analyses of brain activity and performance during *n*-back (1/2/3-back) were executed. This task enables manipulation of executive demand, which permits examination of how individual differences in executive functioning can be mapped to functional brain changes. Relative to a young high-

performing group, capacity constraints in executive functioning were apparent between 1–2-back for the elderly participants and between 2–3-back for a young low-performing group. Capacity constraints in neural activity followed this pattern by showing a monotonically increasing response in the parietal cortex and the thalamus for young high performers, whereas activity levelled off at 1-back for elderly performers and at 2-back for young low performers. The response in the dorsal frontal cortex followed a similar pattern. Together, these findings indicate that fronto-parietal as well as sub-cortical areas are important for individual differences in executive functioning, training of updating and transfer effects.

Key words: cognitive training, executive functioning, transfer, fMRI, brain system, young adults, elderly, practice, neural correlates, individual differences

Acknowledgements

I would like to express my gratitude to everyone who in various ways has been there for me and made these years such a nice and pleasant time to remember. First, big thanks to my supervisors Lars N and Anna for being the quintessence of what supervisors should be. Thanks for your enthusiasm and kind personal support. I also wish to express my gratitude to Lars B. In particular, thanks for reading and providing outstanding comments on all the papers included in this thesis. This work would not have been possible without the interesting meetings with and the financial support from the Nordic Center of Excellence in Cognitive Control, thanks! I am also grateful to all the participants in the project in which this work was undertaken.

Moreover, I would like to thank the staff at IMB where there is always a pleasant atmosphere. In particular, thanks to Ingalill, Anna-Lena, Anita, Anders, Göran, Erland, Tuija, K-G, and Risifrutti-Lennart, for discussing matters marginally related to work during lunch breaks. Thanks Anna for trying to go to IKSU with me and being an appreciated friend. C-J, thanks for always listening to my talks about new apartments with great potential, and for being my verbal dictionary of synonyms. I would also like to take the opportunity to thank the members of the UFBI lab-group Johan, Gregoria, Per, Kristiina, Daniel, Alireza, Karolina, Sara and others for our interesting Tuesday lab-meetings. Big thanks to Micael for DataZ and MatLab tips, to Anne and Ann-Catrine for help during brain data collection, and to Andrew for programming the training program. Thanks also to Linus, Petra, Erik, and others in the cognitive science PhD group, and for stimulating discussions on various topics mixed with the obligatory cake.

My friends-outside-office have also been important. Thanks Erika, for stimulating conversations about life in general, hopes and dreams in particular. Ida, Åsa and Karin for being such good study partners back when we started at the University, and for still being really good friends! The old "gang" from Sundsvall (you know who you are...) - I am so glad we still have such good contact, you are very important to me!

I am also very grateful to my family for your care and encouragement. Thanks to my mother Eva for calling daily, to my father Håkan for many enjoyable lunches in Umeå, and to my sisters Anneli and Carina with families for your love and support. I also want to thank all "new" family members (Lillemor, Eilert, Lena, Anna + family, Barbro, Bosse, and Björn) for always being there: I am glad you have come into my life!

Finally, I would like to thank Hans, for your love, support and singing in the mornings. Love you!

Umeå, October 2009
Erika Dahlin

List of publications

This doctoral thesis is based on the following three papers. They will be referred to by their roman numerals.

- I. Dahlin, E., Stigsdotter Neely, A., Larsson, A., Bäckman, L. & Nyberg, L. (2008). Transfer of Learning after Updating Training Mediated by the Striatum, *Science*, 320(5882), 1510-1512.
- II. Dahlin, E., Nyberg, L., Bäckman, L. & Stigsdotter Neely, A. (2008). Plasticity of Executive Functioning in Young and Old Adults: Immediate Training Gains, Transfer, and Long-Term Maintenance, *Psychology and Aging*, 23(4), 720-730.
- III. Nyberg, L., Dahlin, E., Stigsdotter Neely, A. & Bäckman, L. (2009). Neural Correlates of Variable Working Memory Loads Across Adult Age and Skill: Dissociative Patterns within the Fronto-parietal Network, *Scandinavian Journal of Psychology*, 50(1), 41-46.

All papers are reproduced with the permission of the copyright holders.

Table of Contents

INTRODUCTON.....	1
Executive functioning.....	1
<i>The neural basis of executive functioning.....</i>	2
<i>The taxonomy of executive functioning.....</i>	3
Neural systems underlying updating.....	4
<i>Cortical areas underlying updating.....</i>	5
<i>Sub-cortical areas underlying updating.....</i>	6
Training effects.....	8
<i>Changes in performance following training.....</i>	9
<i>Neural changes following training.....</i>	11
<i>Long-term maintenance of training.....</i>	12
<i>Transfer effects.....</i>	12
Executive functioning and individual differences.....	14
<i>Neural basis of individual differences.....</i>	15
GENERAL AIM.....	17
GENERAL METHODS.....	18
Participants.....	18
Updating training.....	19
Pre- and post-testing.....	21
The fMRI neuroimaging technique.....	23

OVERVIEW OF EMPIRICAL STUDIES.....	25
Study I.....	25
Study II.....	28
Study III.....	30
GENERAL DISCUSSION.....	32
Improvement in performance following updating training.....	33
Neural changes following updating training.....	35
Improvement on transfer tasks following updating training.....	37
<i>Behavioural transfer effects</i>	37
<i>Neural correlates in transfer tasks</i>	38
Long-term maintenance following updating training.....	39
Individual differences in executive functioning.....	41
<i>Individual differences in relation to training data</i>	41
<i>Individual differences in relation to brain mapping</i>	43
<i>Is it possible to generalize the outcome for other groups of participants?</i>	45
Limitations and future directions.....	46
CONCLUDING REMARKS.....	48
REFERENCES.....	49

INTRODUCTION

BEEP, BEEP, BEEP, BEEP... I woke up to the annoying sound of the alarm clock after a bad night's sleep. Still tired I fell asleep again. Finally waking up at eight, I remembered the important meeting set for 8.30 and hastened off to the bathroom for a brief shower. After the shower I put some bread in my bag to eat on the way to work, and ran to the car. "No car keys?!". Irritated, I went back home to find them. Getting more and more panicky and not finding them anywhere I decided to walk instead. Finally at work, I put my hand in my pocket only to recognize that the keys had been there all the time. Of course, the meeting was a disaster. No matter how hard I tried to focus on the information, I kept hearing my colleagues in the corridor discussing their weekend plans. Finally, while sitting in my office, I suddenly remembered that I'd left my bag, with my breakfast in it, at home. What a terrible morning!

The reason for including the above description in my doctoral dissertation thesis is that the stressful situation (and probably also the bad night's sleep) decreased my executive functioning. The aim of this thesis is to increase the understanding of executive functioning by investigating the underlying neural correlates, the training of, and individual differences in, executive functioning. The thesis is divided into three main parts. In the first section, I will give a theoretical overview of previous research within the field. In the second section, I will walk through results from each paper included in the thesis, and finally, in the last section I will discuss the findings in relation to previous studies.

Executive functioning

Executive functioning is necessary for higher order cognition such as planning, impulse control and the ability to reach a goal. These functions are central to many everyday tasks such as reading a newspaper or planning the day's activities. Temporary failure in

executive functioning is a common occurrence for all and can be both irritating and time-consuming. More permanent declines in executive functioning do however cause more serious problems commonly occurring in the elderly, patients with attention-deficit hyperactivity disorder (ADHD), Parkinson's disease, stress disorders, etc. (Mateer, 1999).

The neural basis of executive functioning

Research on executive functioning and its neural correlates has increased markedly over the past five years, but the theoretical and empirical work was started much earlier by the Soviet psychologist Alexander Luria (1902-1977). His theories of brain function were a result of his work with World War II veterans showing various forms of traumatic brain injuries (Luria, 1979). Using his systematic approach, he proposed that the frontal lobes were responsible for planning, initiating, regulating and verifying behaviour. He specifically suggested that the prefrontal cortex supported the highest levels of cognitive organization, and described this area as a central executive (Luria, 1966). Even today, the frontal lobes are believed to play a critical role in the control processes Luria described, and there are several studies demonstrating impaired performance in a large range of executive tasks in patients with brain damage of the frontal areas (Burgess & Shallice, 1996; Mateer, 1999; Owen, Downes, Sahakian, Polkey, & Robbins, 1990). However, patients with lesions outside frontal areas also demonstrate executive impairments (Kramer, Reed, Mungas, Weiner, & Chui, 2002), and executive functioning thus seems not to be restricted to the frontal lobes (Gazzaniga, Ivry, & Mangun, 2002). A recent review investigating neural correlates of executive functioning in monkeys indeed revealed that the frontal as well as the parietal cortex were core regions for executive functioning (Stoet & Snyder, 2009). In line with this, an additional review focusing on functional neuroimaging studies in humans revealed executive functioning to distributed neural networks involving interactions between prefrontal and posterior regions (Collette & Van der Linden, 2002).

The taxonomy of executive functioning

Most researchers agree that executive functioning is necessary for higher cognitive tasks but there is a lack of consensus regarding the taxonomy. While Posner used the term *cognitive control* and recognized that there is a separate executive branch of the attentional system which is responsible for focusing attention on selected aspects of the environment (Posner & Petersen, 1990), Baddeley proposed a similar system as part of his model of working memory (Baddeley, 1986) and called it *the central executive*. Baddeley refers to working memory as the ability to hold and monitor information during a short delay and this includes the ability to simultaneously store and manipulate information (Baddeley, 1996). Working memory consists of three components according to the original model: one is specialized for maintenance of speech-based information (the phonological loop), one is specialized for maintenance of visual information (the visuospatial sketchpad), and in addition to these two slave systems, the model also includes a control structure (the central executive).

Moreover, there is a lack of consensus regarding the number of sub-components of executive functioning. Smith and Jonides (1999) distinguished between mechanisms related to *attention and inhibition, task management, planning, monitoring, and encoding*, but one year later, Akira Miyake and colleagues (2000) published a paper with a new classification defining three sub-components of executive functioning. A study where more than one hundred college students performed a set of experimental tasks which were all considered to tap different executive functions (Miyake et al., 2000) provided evidence for a division of executive functioning into three separate, but moderately correlated, functions: *updating, shifting* and *inhibition* (Fig 1). Miyake and colleagues defined updating as a function that updates and monitors working memory representations, shifting as a function responsible for attention or task shifting, and inhibition as the ability to deliberately inhibit dominant, automatic, or prepotent responses. The theoretical model by Miyake et al. (2000) serves as background to the work presented in this thesis. In particular, the

work focuses on updating which is one of the most central executive functions, and intervenes in a large number of everyday activities, such as the learning and organization of recently acquired information (Miyake et al., 2000; Shimamura, 2000). Updating has also been correlated to intelligence (Friedman et al., 2006) and is therefore important in complex cognition in a more general sense. Based on these findings, updating seems to be a prime candidate to be addressed in the studies included in this thesis.

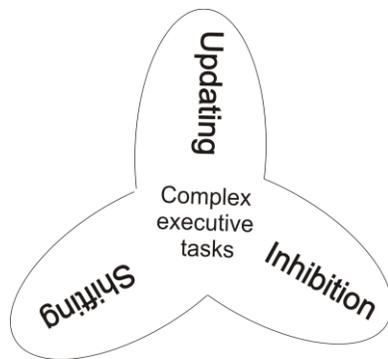


Figure 1. *Updating, shifting and inhibition* are all involved in complex executive tasks but still three separable executive functions. These functions have been described as three separate functions moderately correlated to each other.

Neuronal systems underlying updating

Updating consists of continuously modifying the content of working memory according to newer incoming information and has been explored with the running span (Salmon et al., 1996; Van der Linden et al., 1999) and *n*-back task (Braver et al., 1997; Jonides et al., 1997; Schumacher et al., 1996; Smith, Jonides, & Koeppe, 1996). In the running span task, participants are required to watch strings of items of unknown length, and then they have to remember a specific number of recent items in serial order. In *n*-back, items are sequentially presented and subjects have to decide whether a given item is similar to the one presented *n* items previously.

Cortical areas underlying updating

After reviewing brain imaging studies including e.g., the running span and *n*-back task have evidence that the specificity and commonality of executive functioning reported at the cognitive level (Miyake et al., 2000) also been reported at the cerebral level (Collette, Hogge, Salmon, & Van der Linden, 2006). A distributed anterior-posterior cerebral network specific for updating, involving prefrontal cortex (e.g., BA 10 and BA 9/46), has been identified (Jonides et al., 1997; Salmon et al., 1996; Smith et al., 1996; Van der Linden et al., 1999) after reviewing updating, shifting and inhibition imaging studies with the aim of identifying neural systems specific for each function (Collette & Van der Linden, 2002). Two PET studies have directly investigated neural correlates underlying updating per se with a starting point in the model by Miyake et al. (2000). A bilateral network of prefrontal, parietal and cerebellar regions was found to sub-serve performance on updating independently of stimuli type when serially presented items (consonants, words, or sounds) of unknown lengths were presented to participants who were instructed to recall the last four items presented at the end of the presentation (Collette et al., 2007). When comparing brain activation during performance of the same updating tasks, to brain activity related to inhibition or shifting tasks, it was found that the anterior prefrontal cortex (BA 10) was associated with updating but not with inhibition or shifting (Collette et al., 2005).

In addition, a meta-analysis revealed that updating was associated with several frontal as well as parietal areas. The superior parietal cortex (BA 7) was associated with executive functioning in general (including updating), whereas the anterior prefrontal cortex (BA 10) was associated with updating per se (Wager & Smith, 2003). Altogether, the findings described above highlight the frontal and parietal cortex as core regions in updating, and especially the anterior prefrontal cortex (BA 10) seems to be a prime area underlying updating per se.

Sub-cortical areas underlying updating

Both frontal and parietal areas have also been included in theoretical models critical to cognitive functioning. A parallel organization of functionality in segregated circuits linking basal ganglia and the cortex has been described by Alexander, DeLong, & Strick (1986). According to this model, the dorsolateral prefrontal circuit consists of at least two distinct basal ganglia-thalamocortical circuits that selectively influence separate prefrontal areas. Projections arise from the dorsal prefrontal cortex (BA 10) and posterior parietal cortex (BA7) to the striatum and the circuits then continue to the globus pallidus and the substantia nigra (parts of the basal ganglia). In turn, these regions project to the thalamic nuclei, which project back to the prefrontal cortex.

The extensive connectivity between the frontal cortex and the basal ganglia have also been described in computational models of higher level aspects of human intelligence based on the biology of the brain (O'Reilly, 2006). It is reported that updating of the prefrontal cortex appears to be satisfied by dynamic gating mechanisms which can be explained as follows: when a gate is open, the prefrontal cortex is rapidly updated with new information and when the gate is closed, it robustly maintains existing information. It is reported that direct pathways in the basal ganglia can trigger a phasic wave of activation into the prefrontal cortex that results in rapid updating. Hence, this model suggests that the basal ganglia serve as a selective dynamic gating function that enables frontal memory representations to be rapidly updated, whereas the frontal cortex is instead responsible for active maintenance of information (O'Reilly, 2006). In light of these models I wanted to investigate whether fMRI imaging studies also report basal ganglia and striatal activation during updating performance. A literature search on Medline identified relevant studies. Studies were included if *updating* was included in the abstract, and *fMRI*, and *basal ganglia* or *striatum* were included in all the texts (Table 1). Since cortical findings in relation to updating are already reported above, the focus is on sub-cortical findings in Table 1.

Table 1.

Overview of fMRI studies reporting sub-cortical involvement in updating

Study	Contrasts	Basal ganglia		
		Striatum	GPI	Thalamus Cerebellum
Dyckman et al (2007) <i>Neuroimage</i>	saccade task > null condition	B		B
Marklund et al (2009) <i>Brain</i>	2-back word task > fixation	B	B	
Tan et al (2007) <i>J Neurosci</i>	Num computational > retrieval	B		B
Tinaz et al (2006) <i>Brain research</i>	object discrimination > control task		B	
Tunik et al (2009) <i>Neuroimage</i>	viscous updating > null condition	L		R

Note. L = Left; R = Right; B = Bilateral; GPI = Globus Pallidus

From the literature search, I found that activity in basal ganglia has been reported in previous studies during the performance of tasks requiring updating measured with fMRI (Table 1). However, all the studies found did not investigate updating per se even if updating always was involved to a certain extent. For example, brain activity was related to more general executive processes such as response selection and/or context updating, when participants focused on a target and looked at the opposite side of the screen when the cue moved to a peripheral location (Dyckman, Camchong, Clementz, & McDowell, 2007). Brain activity was related to remembering numbers and computing or rapidly updating relevant numbers when participants made a numerical size judgment in combination with numerical subtraction (Tan et al., 2007). And moreover, brain activity related to ordering a series of pictures required updating to a greater extent compared to the identification of an odd item among a set of objects (Tinaz, Schendan, Schon, & Stern, 2006).

Two studies listed in Table 1 isolated the updating to a greater extent. Updating from non-viscous to a positive viscous torque during motor decision-making processes revealed activity in both the striatum and the cerebellum (Tunik, Houk, & Grafton, 2009), and updating of working memory revealed activity in two basal ganglia nuclei (Globus pallidus and striatum; Marklund et al., 2009). Moreover, a comparison of Parkinson's disease patients to age-

matched controls revealed that healthy controls had more activity in both the striatum and the globus pallidus and the authors suggest that the under-activity in Parkinson's disease patients might be related to phasic mechanisms underlying updating (Marklund et al., 2009). Altogether, even if not all studies listed in Table 1 investigated updating per se, the updating process was involved to at least some extent in all studies and striatal activity was suggested to underlie updating in both motor and cognitive task.

Functionally the striatum has been divided into three different compartments; sensimotor, associative and limbic (Cervenka, Bäckman, Cselényi, Halldin, & Farde, 2008; Martinez et al., 2003). Martinez et al. (2003) describe the sensimotor compartment primarily involved in motor definition, the associative striatum involved in cognitive processing, and the limbic compartment implicated in drive and motivation. In addition, recent studies indicate that the limbic striatum is involved in memory and executive performance as well (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Cervenka et al., 2008).

Training effects

Given the importance of *updating* in everyday cognitive activities (Miyake et al., 2000; Shimamura, 2000), it is striking that relatively little interest has been paid to the potential modifiability of this function per se. However, some studies have investigated the training of working memory and executive functioning in general. Training-related improvements have been found following the training of both working memory and executive functioning in, for example, the elderly (Kray & Epplinger, 2006), children with ADHD (Klingberg, Forssberg, & Westerberg, 2002), stroke patients (Westerberg et al., 2007), and schizophrenia patients (López-Luengo & Vázquez, 2003). Here I will focus on results from young healthy subjects, and a brief overview of the training studies that I will then go through can be found in Table 2.

Table 2.

Overview of recent studies in young healthy subjects including working memory and executive training

Study	Training task	Training period	Transfer to	Maint-	Fronto-	Sub-
				enance	parietal	cortical
Bherer et al (2005) <i>Psychol Aging</i>	dual-task processing	5 S, 3 W	dual-task, new-stimuli	-	-	-
Bherer et al (2008) <i>Exp Aging Res</i>	dual-task processing	5 S, 3 W	dual-task, new stimuli within modality	-	-	-
Brehmer et al (2008) <i>Poster CAC</i>	spatial and verbal WM	daily, 5 W	-	-	↓	n.s.
Erickson et al (2007) <i>Cereb Cortex</i>	dual-task processing	5 S, 2-3 W	-	-	↓	n.s.
Gaab et al (2006) <i>NeuroImage</i>	pitch memory	5 S, 5 D	-	-	↓	↑
Hempel et al (2004) <i>Am J Psychiatry</i>	spatial n-back	daily, 4 W	-	-	↑↓	-
Jaeggi et al (2008) <i>PNAS</i>	dual n-back	8,12,17 or 19 D	fluid intelligence	-	-	-
Jansma et al (2001) <i>J Cogn Neurosci</i>	verbal WM	tot 45 min, 4 S	-	-	↓	n.s.
Karbach & Kray (in press) <i>Dev Sci</i>	task-switching	4 S, 4 W	interference control, fluid intelligence, auditory discrimination	-	-	-
Kramer et al (1999) <i>Acta Psychol</i>	task-switching	4 S, 1 W	-	2 M	-	-
Li et al (2008) <i>Psychol Aging</i>	spatial shifting and updating	daily, 45 D	spatial shifting and updating	3 M	-	-
McNab & Klingberg (2009) <i>Science</i>	WM tasks	~24 S, 5 W	overall WM capacity	-	↑&↓	n.s.
Minear & Shah (2008) <i>Mem Cognition</i>	task-switching	2 S, 2 D	task-switching	-	-	-
Olesen et al (2004) <i>Nat Neurosci</i>	spatial WM	~20 D, 5 W	inhibition, WM capacity, fluid intelligence	-	↑	↑
Westerberg et al (2007) <i>Physiol Behav</i>	WM tasks	~25 D, 5 W	WM and reasoning	-	↑	n.s.

Note. S = Session; D = days; M = Months; ↑ = increased training-related activity; ↓ = decreased training-related activity; n.s. = no significance; - = not investigated

Changes in performance following training

A lot of previous research has focused on the training of working memory (Table 2) and results reveal the possibility of increasing working memory capacity after five weeks of spatial and verbal working memory training (Brehmer, Westerberg, Rieckmann, Fischer, & Bäckman, 2008; McNab & Klingberg, 2008; Olesen, Westerberg, & Klingberg, 2004; Westerberg & Klingberg, 2007). Reduced reaction times have also been found following four training sessions in which

the participants memorized consonants in order to decide whether the presented consonants belonged to the target or not (Jansma, Ramsey, Slagter, & Kahn, 2001).

The executive function that has received most attention of the functions proposed in the model by Miyake et al., (2000) is the modifiability of shifting. A paradigm strongly connected to executive functions in general and shifting in particular is the dual-task paradigm, where participants are instructed to execute two tasks in parallel. Reduced reaction times in the trained tasks have been shown after five sessions of dual-task training (Bherer et al., 2005, 2008; Erickson et al., 2007). Another paradigm where shifting is necessary is task-shifting, where the participants are instructed to shift attention between two relatively simple tasks e.g., to indicate whether a digit is odd or even, and to indicate whether a letter is a vowel or consonant. An observation frequently made in task-shifting paradigms is that when people switch between two tasks, their performance is worse than when they perform each task in isolation (Rogers & Monsell, 1995). This is indicated by a shift cost, which means that the response time (RT) is slower on switch trials (A to B or B to A) than on repeated trials (A to A or B to B). Reduction in shift cost has been found following both four (Karbach & Kray, in press; Kramer, Hahn, & Gopher, 1999) and five (Gaab, Gaser, & Schlaug, 2006) sessions of task-shifting training. Comparing random shift training to predictable shift training has shown reduced shift costs following training with a trend toward larger reductions with practice for the random training group (Minear & Shah, 2008).

Training of tasks involving updating has not been frequently investigated (Table 2). One study investigated training of both spatial shifting and updating (Li et al., 2008) and found that 45 days of daily training improved performance in the trained tasks. The training tasks included were a spatial *n*-back task and an *n*-back task in which participants were instructed to mentally shift the presented position one step clockwise and memorize the shifted position. In another study there was a dual *n*-back task trained for 8, 12, 17, or 19 days. The training task involved dual task performance and consisted of

simultaneous presentations of auditory presented consonants and visual squares in different positions. The participants were then instructed to decide whether the stimuli were similar to the stimuli presented n stimuli back. They found that groups receiving more training showed larger gains compared to groups receiving less training (Jaeggi, Buschkuhl, Jonides, & Perrig, 2008). Even if both Li et al. (2008) and Jaeggi et al. (2008) investigated training of tasks involving updating, only one previous study has investigated training of updating per se. They found a decreased error rate following 4 weeks of daily training on a spatial n -back task for four weeks, which indicates that it is possible to modify updating following direct training, at least in young healthy subjects (Hempel et al., 2004).

Neural changes following training

In view of the previous review of neural correlates highlighting fronto-parietal and sub-cortical areas as core regions underlying executive functioning, it is interesting to look at these areas in relation to training. Fronto-parietal training-related increases have been most frequently reported after training on the working memory (Olesen et al., 2004; Westerberg & Klingberg, 2007), but training-related decreases have also been reported in these regions (Brehmer et al., 2008; Jansma et al., 2001). Following training of the executive function shifting, have fronto-parietal training-related decreases been most frequently reported (Erickson et al., 2007; Gaab et al., 2006). The most common pattern after both repeated exposure to executive tasks (Chein & Schneider, 2005) and more extensive training (Kelly, Foxe, & Garavan, 2006; Kelly & Garavan, 2005) is actually decreased activity in fronto-parietal regions.

Two studies have also reported changes in sub-cortical areas such as the striatum and the cerebellum after training (Gaab et al., 2006; Olesen et al., 2004). Both these studies reported increased sub-cortical activity after training (Table 2) and hence, training-related changes in both fronto-parietal and sub-cortical areas have been reported after training of the working memory and executive functioning.

Long-term maintenance of training

Long-term effects should be an important goal of all training interventions. Unfortunately, there are only a few studies highlighting the topic following the training of working memory and executive functioning in young adults (Dahlin, Bäckman, Stigdotter Neely, & Nyberg, in press). Two previous studies have investigated training of executive functions including testing of long-term maintenance (Table 2) and reported that training effects can be maintained 2 months post-training following task-shifting training (Kramer et al., 1999) and maintained 3 months post spatial shifting and updating training (Li et al., 2008) in young adults. No previous training study of updating per se has investigated long-term maintenance.

Transfer effects

The ultimate goal of all cognitive training is to achieve effects, not only on trained, but also on untrained tasks i.e., transfer effects. Applying what we have been trained to do to different contexts, and extending learning to completely new situations, are important in our everyday life. Despite the relevance of transfer effects, this area still remains poorly studied (Table 2) and studies investigating transfer effects typically reveal patterns of limited generalization despite a large improvement in the trained task itself (Dahlin et al., in press).

The most common finding in studies documenting transfer effects is however improvements in tasks similar to the trained task (Table 2). For example, transfer effects have been found in tasks where high working memory capacity was necessary following five weeks of working memory training (Olesen et al., 2004; Westerberg & Klingberg, 2007) and following dual *n*-back training to fluid intelligence (Jaeggi et al., 2008), reflecting that working memory and fluid intelligence share attentional control processes. Moreover, substantial transfer effects have been reported within modality (visual), but limited effects have been reported cross-modality (auditory) following visual dual-task training (Bherer et al., 2008), which sets limits on the nature of transfer between modalities.

A frequently discussed factor in the context of transfer effects is the relation between trained and transfer tasks. As early as in 1901, Thorndike and Woodworth (Thorndike & Woodworth, 1901) found that training in one task caused an improvement in performing another transfer task. Participants were trained to estimate areas of a specific shape and improved in performance after training. Effects on transfer tasks were also found, but the effect was more pronounced when areas were similar in shape to those in the training series, compared to when new shapes were used. Moreover, the improvement differed, depending on the level of similarity between the trained and transfer tasks, and gains could be attributed to common elements in the trained and transfer tasks. As a result of the paper by Thorndike and Woodworth, the terms *near-* and *far-*transfer were introduced in the literature. Near-transfer tasks are described as transfer tasks that are similar to the trained task, whereas far-transfer tasks are described as transfer tasks that have less in common with the trained task.

To classify a task as near- or far-transfer can, however, be a complex undertaking; the designations are used inconsistently by different researchers and findings show that expectations based on similarities between the obvious surface elements can be completely incorrect. For example, it is reported that there was very little transfer of gains in performance following practice with one set of stimuli (a set of 10 letters) to a second set of stimuli (a second set of 10 letters) in an alphabetic-arithmetic task (e.g., $A + 2 = C$), even if the elements were almost identical (Logan & Klapp, 1991).

Altogether, the relation between the trained and transfer task may be important for transfer but there is no consensus on how similar the tasks should be to make it possible to find transfer. With regard to the previously described model of three separate, but moderately correlated, executive functions (Miyake et al., 2000), it should be interesting to investigate whether training of e.g., updating transfer to executive functioning in general or whether transfer is limited to updating per se. Moreover, the fact that researchers have not found any solution to the transfer question despite one hundred

years of investigations makes it justifiable to search for the answer elsewhere. It has been hypothesized that overlapping networks or brain areas for trained and transfer tasks are necessary for producing transfer effects (Jonides, 2004), and knowledge about neural correlates of transfer may shed further light on underlying mechanisms. No previous studies have investigated transfer effects from a neural perspective, but based on the foregoing review of neural systems underlying updating, our hypothesis is that transfer effects following updating training may be mediated by either a general fronto-parietal cortical system (c.f. Klingberg et al., 2005) or a more specific striatal system (c.f. Miyake et al., 2000). Our suggestion is that transfer effects to a more distributed set of tasks will be found if transfer effects are mediated by the fronto-parietal cortical system as opposed to the striatal system.

Individual differences in executive functioning have been found to influence the degree of transfer after training on, for example, a visual comparison task (Sohn, Doane, & Garrison, 2006), and hence a key aspect when discussing training and transfer effects is the differences in executive functioning between groups or individuals.

Executive functioning and individual differences

Previous studies have revealed that there are differences in performance between a high working memory span and a low working memory span group (Osaka et al., 2003; Osaka et al., 2004), and that short-term capacity limits vary substantially across individuals (Vogel, McCollough, & Machizawa, 2005). Moreover, previous studies have shown that individual differences in updating can influence the ability to solve arithmetic problems (Passolunghi & Pazzaglia, 2004), and there is evidence that the degree of transfer after training varies with individual differences in cognitive ability (Sohn et al., 2006). These findings suggest that there exist individual differences in higher order cognition and executive functioning. These differences can be magnified by advanced age or disorders. For example, several studies

showed that executive functioning is negatively affected in later adulthood (Kray & Lindenberger, 2000; Salthouse & Babcock, 1991; Van der Linden & Bredart, 1994).

Investigation of individual differences in executive functioning can be done by manipulation of the level when a task becomes executively demanding. One way of finding the load at which the task becomes executively demanding and the capacity is constrained (which differs between individuals) is to heavily tax the working memory capacity. In previous studies, the running span or *n*-back task has been used to investigate how the brain maps to different levels of executive demands. The load has been manipulated by varying the number (0/1/2/3 back) of letters (Braver et al., 1997; Cohen et al., 1997) or numbers (Callicott et al., 1999) between the target and presented stimuli, or by varying the numbers of presented objects (1-4) during encoding (Linden et al., 2003) in a visual discrimination task. These tasks have also been used during fMRI scanning as the neural basis for limitations in executive functioning has attracted much interest in recent years.

Neural basis of individual differences in executive functioning

With regard to the previous review of neuroimaging studies, the next natural question is whether the source of individual differences in executive functioning is also found in the fronto-parietal and sub-cortical areas. The basic idea when investigating the neural basis for limitation in executive functioning is to determine how brain activity changes as a function of parametric manipulation of demand (Cohen et al., 1997). In previous research two major mapping functions have been found and reflect *capacity-unconstrained* responses where brain activity increases linearly as a function of increased load (Fig 2a), and *capacity-constrained* responses where brain activity increases up to a certain level and then decreases (Fig 2b).

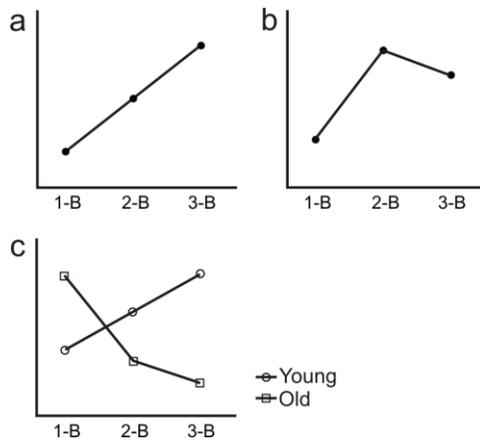


Figure 2. Manipulations of n in n -back have revealed both (a) capacity-unconstrained responses and (b) capacity-constrained responses in brain activity changes. (c) The mapping function between load and brain activity typically differs between younger and older adults with older adults showing greater activation than younger adults at low load with a reversed pattern at higher load.

Capacity-unconstrained responses in brain activity across load are reported in the dorsal prefrontal cortex (Braver et al., 1997) and the parietal cortex (Braver et al., 1997; Cohen et al., 1997). However, capacity-constrained brain activity across load is also reported in the dorsal prefrontal cortex and the parietal cortex (Callicott et al., 1999). In still another study (Linden et al., 2003) a capacity-unconstrained response was found in the dorsal prefrontal cortex, whereas activity in various parietal and frontal regions followed a capacity-constrained response. The findings reported above are conflicting, which makes it difficult to draw firm conclusions about the neural basis of individual differences in executive functioning. To further complicate matters, it is reported that the mapping function between load and brain activity differs between younger and older adults (Mattay et al., 2006). In the dorsal frontal cortex older adults showed greater activation than younger adults at a low load. At higher loads the pattern was reversed due to a monotonic decreasing trend for older adults along with an opposite tendency for younger adults (Fig 2c).

GENERAL AIM

Based on the foregoing review, the general aim of this thesis was to further investigate how neural changes are related to variations in working memory load and how the training of executive functioning affects performance and brain activity in trained and transfer tasks. The main issues to be addressed may be summarized as follows:

- (1). Will updating performance be improved by direct training? (Study I and II)
- (2). How will neural changes be related to enhanced performance after updating training? (Study I)
- (3). Does updating training facilitate improvements in performance in transfer tasks? (Study I and II)
- (4). Will transfer effects depend on more general or more specific neural overlap? (Study I)
- (5). Will increased performance following updating training be maintained over time? (Study II)
- (6). Are there individual differences in executive functioning and how can these be mapped to functional brain changes? (Study I, II, and III)

GENERAL METHODS

Participants

Studies I-III include sub-samples of data collected from 32 young participants (mean age 24.00; range 20-31) and 32 older adults (mean age 68.31; range 65-71). Young participants were recruited through e-mail to students at Umeå University, Sweden, and older participants were recruited through newspaper advertisements in a local daily newspaper. All participants were individually tested at a pre-test, and a post-test session. Six young (2 training, 4 controls) and 3 older (all training) participants dropped out and are therefore not included in the final analyses. Analyses of background characteristics revealed no significant differences between those remaining in the study and the dropouts within each particular age group. The distribution of included subjects can be found in Table 3. The training and control participants in each age group did not differ significantly ($p > .05$) with respect to age, years of education, depression (Beck & Steer, 1996), verbal ability (Dureman & Sälde, 1959), or mental status (Folstein, Folstein, & McHugh, 1975). All participants reported being in good psychical and mental health, not colour blind, and right-handed. All participation was voluntary, and

Table 3.
Subject characteristics (M ± SD) Study I-III

	Study I				Study II				Study III			
	Young		Old		Young		Old		Young		Old	
	trained	controls	trained	controls	trained	controls	trained	controls	low	high	low	high
Female/Male	8/7	2/5	7/4	6/2	8/7	4/7	7/6	11/5	6/5	4/7	9/2	9/2
Age	23.7 ± 2.9	23.4 ± 1.3	68.3 ± 1.8	68.4 ± 1.9	23.7 ± 2.9	24.1 ± 2.1	68.4 ± 1.7	68.3 ± 1.7	23.6 ± 2.9	23.6 ± 2.1	68.8 ± 1.5	68.8 ± 1.5
Years of education	13.4 ± 1.4	13.4 ± 0.7	14.6 ± 3.6	12.4 ± 2.6	13.4 ± 1.4	13.8 ± 1.9	14.5 ± 4.1	12.0 ± 3.0	13.4 ± 1.4	13.5 ± 1.0	15.0 ± 2.4	15.0 ± 2.4
Depression (a)	3.4 ± 3.3	5.0 ± 2.9	3.6 ± 3.3	6.5 ± 4.0	3.4 ± 3.3	3.6 ± 3.3	3.5 ± 3.2	6.3 ± 4.4	3.5 ± 3.2	4.4 ± 3.2	3.9 ± 2.3	3.9 ± 2.3
Verbal ability (b)	22.7 ± 2.6	20.9 ± 3.8	22.7 ± 4.8	23.9 ± 4.4	22.7 ± 2.6	22.1 ± 3.6	22.4 ± 5.0	23.3 ± 3.8	22.3 ± 3.6	21.9 ± 2.6	24.9 ± 3.7	24.9 ± 3.7
Mental status (c)	29.0 ± 0.9	29.3 ± 0.8	28.7 ± 0.9	28.8 ± 0.7	29.0 ± 0.9	29.2 ± 0.9	28.7 ± 1.0	28.8 ± 0.7	29.1 ± 0.7	29.1 ± 1.0	28.9 ± 0.7	28.9 ± 0.7

Note. (a) Beck Depression Inventory (Beck & Steer, 1996); (b) SRB1 (Dureman & Sälde, 1959), maximum score = 30; (c) Mini-Mental State Examination (Folstein et al., 1975)

the studies were approved by the ethics committee of Umeå University.



Figure 3. Photo of participants receiving training in groups of four. The photo is published with the permission of the subjects.

Photo: Erika Dahlin, Umeå.

Updating training

The participants receiving training were invited to participate in 15 sessions during a period of 5 weeks (3 sessions per week). Each session lasted for approximately 45 minutes, and the participants trained in groups of four (Fig 3). The training was computer-based, a format that has been shown to be beneficial for both young and older people (Klingberg et al., 2005; Rasmusson, Rebok, Bylsma, & Brandt, 1999). A training session consisted of practice on five different training tasks which all taxed the executive function updating. Four of the training tasks were similar to each other (Fig 4a-d). In each of these tasks, five lists of single items were presented (letters, numbers, colours, and spatial location) and the participants were instructed to monitor and recall the last four items presented in the correct order when the list presentation ended. To ensure that the tasks remained cognitively challenging throughout the training period, the list length was varied (low level = 4-7 items; medium level = 6-11 items; high level = 5-15 items). The level of difficulty was adjusted when participants scored 80% correctly recalled items on the letter-training task (i.e., 16 letters or more, Fig 4a).

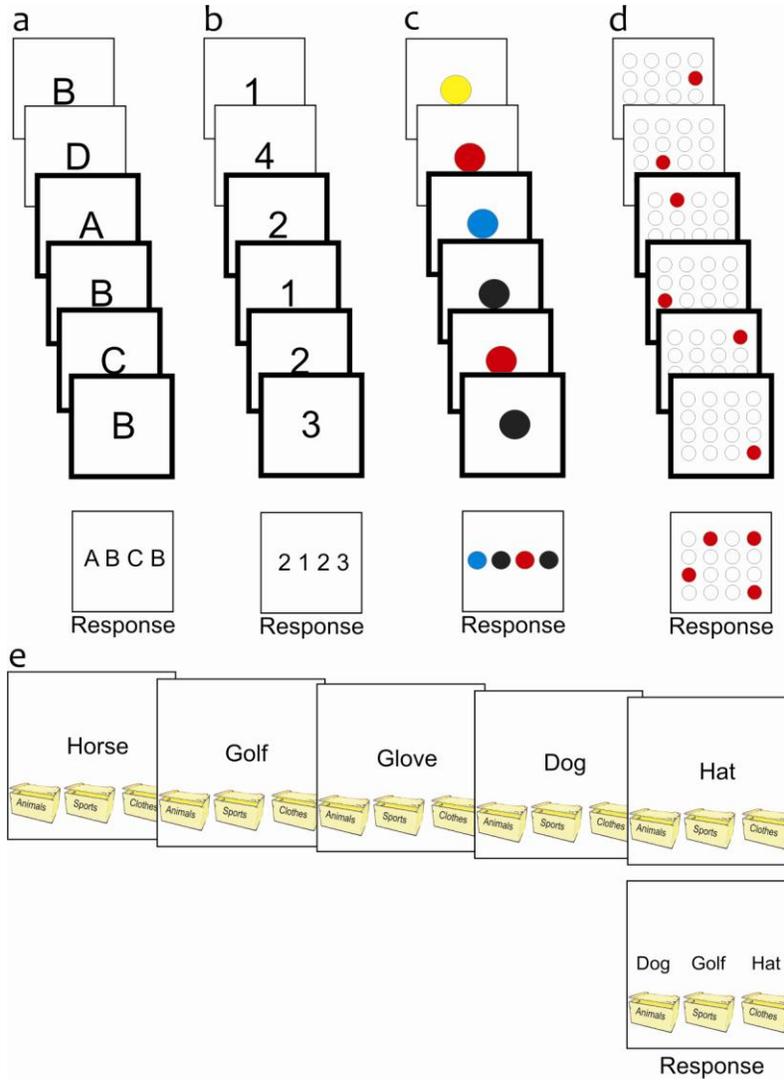


Figure 4. Training tasks included during the five-week training period in study II and III. Training tasks *a-d* were similar to each other: single items were presented (letters, numbers, colours, and spatial locations) and the participants were instructed to monitor and recall the last four items presented. In training task *e* subjects were instructed to mentally place serially presented words into semantic categories indicated by boxes at the bottom of the screen (in this example: Animals, Sports, Clothes), update the content, and remember the word presented last in each category.

The fifth training task, the keep-track task (Fig 4e) required updating, categorization, and association. Participants were instructed to mentally place serially presented words into semantic categories (animals, clothes, countries, relatives, sports, professions) indicated by boxes at the bottom of the screen. Participants had to update the content continuously and remember the word last presented in each category box. The difficulty level was manipulated by varying the number of category boxes presented (low level = 3; medium level 4; high level 5). Participants also performed a letter memory criterion task during each training session. To make it possible to investigate changes in performance as a function of training difficulty, the level was not adjusted in this task. The criterion letter memory task involved 10 lists of the following lengths: 7, 7, 9, 9, 11, 13, 9, 5, 13, and 15 items. Each list consisted of serially presented letters and the participants were asked to monitor and update the last four letters presented during the list presentation. When the list ended, participants were asked to recall and type in the correct order of the last four letters presented as quickly as possible.

Pre- and Post-testing

All participants were tested on cognitive tests before and after the five-week period. The tests included measurements of cognitive domains such as perceptual speed, working memory, episodic memory, verbal fluency, and reasoning (see Table 4 for description).

Forty-one participants (22 young and 19 old) performed the letter memory criterion, *n*-back transfer, and Stroop transfer tasks during pre- and post- fMRI scanning to make it possible to investigate brain activation changes (the remainder did the tasks outside the scanner). The letter memory task was identical to the letter memory criterion task trained participants performed during each training session (described above).

Table 4.

Description of the tasks included pre- and post-test

Test	Cognitive domain	Description of the task
Mini-Mental State Examination*	General cognitive control	30-point questionnaire used to screen for cognitive impairment
Number copying*	Perceptual speed	To copy as many numbers as possible into empty boxes within 30 s
Digit span forward and backward	Working memory	To repeat a sequence of numbers presented, in the same (forward) or reversed order (backward)
Recall of Concrete nouns	Episodic memory	To freely recall as many words as possible after studying a list of 18 serially presented nouns
Digit symbol	Perceptual speed	To copy as many symbols as possible during 90 s according to associations specified in a coding key
Computation span	Working memory	To solve arithmetic problems while holding the final digit from each problem in memory for later recall
Letter fluency	Verbal fluency	To write down as many words as possible beginning with letters F, A, and S during 90 s
SRB 1*	Verbal ability	A Swedish word synonym test
Pattern comparison*	Perceptual speed	To discriminate two patterns as equal or not equal, as many as possible within 30 s
Paired associates	Episodic memory	After studying a serially presented list of 18 pairs of nouns recall the last noun in a pair when given the first noun as a cue
Trial Making Test (Part A & B)*	Shifting	To draw lines to connect circles with numbers in ascending order (Part A), or to alternate between circles with numbers and circles with letters in an ascending pattern (Part B)
Raven's Advanced Progressive Matrices	Reasoning	To find the option that best fitted the missing section in a two-dimensional pattern-matching matrix
Category fluency	Verbal fluency	To write down as many words as possible during 90 s belonging to different categories: provisions, names of animals beginning with the letter S, and professions beginning with the letter B
Letter memory	Updating	To monitor and update the four letters presented last during a serial list presentation
n-back (1/2/3)	Updating/ working memory	To indicate whether each number in a list matched a number that occurred one, two, or three numbers back.
Stroop	Inhibition	To decide which colour each word was written in as quickly as possible

Note. Tests marked with an asterisk (*) were administered only at pre-test to reduce testing time

The *n*-back task consisted of 27 lists; nine 1-back lists, nine 2-back lists, and nine 3-back lists in random order (Callicott et al., 1999). The lists consisted of 10 items (a digit between 1 and 9) and the participants were instructed to indicate whether or not each item in the list matched an item that occurred one, two, or three items previously. The Stroop task consisted of 72 items (an equal number of congruent, incongruent, and neutral words) presented in random order. The task was to decide which colour each word was written in as quickly as possible (See Supplementary Material Study I for more details).

The fMRI neuroimaging technique

We used the functional Magnetic Resonance Imaging (fMRI) technique to investigate brain activity related to training in study I and individual differences in executive functioning in study III. By using fMRI we are not able to directly measure neuronal activity and therefore measure something that is most probably highly correlated with this activity. Since the brain has very few energy buffers, energy has to be transported as glucose and oxygen in the blood stream to the brain. Increased neuronal activity is therefore supported by increased blood flow, and changes in blood flow are believed to be initiated when active neurons release substances that diffuse through the extracellular space and reach nearby blood vessels. An important factor for fMRI is that the haemoglobin molecule has magnetic properties that differ depending on whether or not it is bound to oxygen. Hence, deoxygenated and oxygenated haemoglobin disturbs the magnetic field differently and makes BOLD contrast fMRI possible. The spatial resolution of fMRI is good (1-2 mm) but the temporal resolution is poor (2-3 sec) in relation to most other neuroimaging techniques. This makes it easy to point out the region of activity, but difficult to determine the exact timing of the activation (for more details about fMRI see Huettel, Song, & McCarthy, 2004 or Frackowiak et al., 1997).

To ensure that the collected data included in the analyses have a certain quality, it is necessary to remove artefacts and uninteresting variables from the raw data. This is done in a series of pre-processing steps. The data included in study I and III were corrected for time differences between slices during image acquisition (*slice timing*), and corrected for head movements and distortions (*realignment & unwarping*). To make it possible to generalize the results to the general population, each subject's brain was *normalized* into a standard brain in terms of shape and size. We used the Montreal Neurological Institute (MNI) template as a standard brain, which is based on 152 neurologically healthy adults. The last pre-processing step was *smoothing*. This process involves spatial filtering of the data so that it is spread across neighbouring voxels making comparisons across subjects possible. Once the pre-processing steps had been completed, the data were ready for statistical analyses. The functional images were analysed with Statistical Parametric Mapping Software (SPM2) implemented in Matlab 7.1.

To find task-specific activity, brain activity during two different conditions was compared (*t*-tests). In Study I, task-specific activity was compared to a fixation baseline in the analyses of both letter memory [letter memory – rest] and *n*-back [3-back – rest], and the congruent condition served as a baseline for the incongruent condition in the Stroop task [incongruent - congruent]. To investigate training-related changes in brain activity, we compared task-related activation [activation – baseline] for the pre-training session to task-related activation for the post-training session. Data computed from the local maxima in regions showing pre-post changes were further analysed by group-by-session ANOVAs with repeated measurement of the last factor. A training-specific effect was defined as a region where the activity level for the trained and control group had to be comparable in the first session, along with a selective change in activation level for the training group in the second session (See Study I for p-values, cluster sizes, etc).

To identify regions that were commonly activated for two different tasks, conjunction analyses were executed in both studies I

and III. The conjunction analysis asserted that all contrasts involved were individually significant at a predefined threshold (Nichols, Brett, Andersson, Wagner, & Poline, 2005).

In Study III, we were interested in how individual differences in executive functioning could be mapped to functional brain changes. In order to establish baseline patterns, a conjunction approach was used, and all young individuals were included ([3-back - 1-back] and [1-back - rest]). The brain regions identified were then further analysed in order to find group differences in executive functioning load. ANOVAs with repeated measurement of the last factor were computed on local maxima from regions showing a load-sensitive pattern (See Study III for p-values, cluster sizes, etc).

OVERVIEW OF EMPIRICAL STUDIES

Study I

Dahlin, E., Stigsdotter Neely, A., Larsson, A., Bäckman, L. & Nyberg, L. (2008). Transfer of Learning after Updating Training Mediated by the Striatum, *Science*, 320(5882), 1510-1512.

Previous studies reveal both fronto-parietal increased (Olesen et al., 2004; Westerberg & Klingberg, 2007) and decreased (Brehmer et al., 2008; Erickson et al., 2007; Gaab et al., 2006; Jansma et al., 2001) activity following working memory and executive functioning training. Sub-cortical changes have also been reported (Gaab et al., 2006; Olesen et al., 2004). However, no previous study has investigated brain activity changes in both young and old participants following updating training per se. To conduct brain activity changes in relation to updating training, young and old participants were fMRI scanned before and after a five-week period. Training participants received training between the fMRI scanning sessions. We included trained (letter memory) as well as transfer tasks (*n*-back, Stroop) during fMRI

scanning. To make it possible to investigate the current hypothesis that transfer will occur if the trained and transfer task involves overlapping processing components and engage, at least in part, the same brain regions (Jonides, 2004) were all tasks included known to activate fronto-parietal areas (Collette et al., 2006) and taxed executive functioning to a certain extent (Miyake et al., 2000).

I will report findings from young and old participants separately. For young participants, we found a significantly higher effect size (performance post – pre training divided by pooled standard pre-training) for the training group compared to controls, which means that trained participants improved significantly more in performance from pre- to post-testing, compared to young controls (Fig 5a). Also behavioural results from the 3-back transfer task revealed significantly higher effect size for trained participants compared to the controls (Fig 5a). The 3-back task required updating and hence shared a basic process with the trained letter memory task. No significant transfer effects were found in the remaining transfer task (Stroop), which required inhibition. No previous study has investigated neural correlates underlying transfer effects (Table 2) and the first plan was to test the hypothesis that transfer occurs if the trained and transfer tasks initially engage similar processes and brain circuits. A conjunction analysis including all subjects' pre-training activity revealed joint activation in the left striatum along with common fronto-parietal activation for letter memory and 3-back. A similar conjunction analysis of letter memory and the Stroop task revealed an overlap in fronto-parietal regions, but no overlapping activity in striatal regions.

Analyses of training-related changes revealed relatively greater activation post-training in the left striatum, along with training-related decreased fronto-parietal activity in the trained letter memory task. When training-related changes were analysed in the transfer tasks, increased activity was seen in the left striatum and frontal cortex for 3-back, whereas no significant training-related changes were found in the Stroop task.

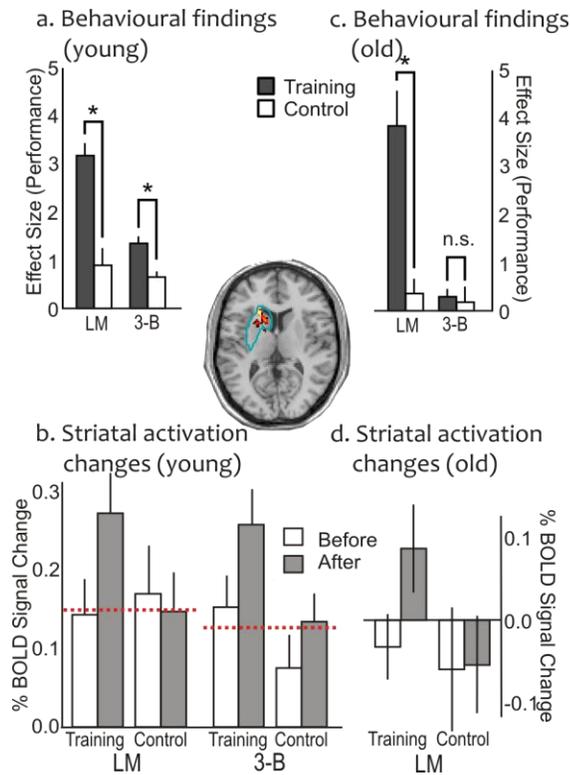


Figure 5. (a) The effect size for young trained participants was significantly higher compared to the controls in the trained letter memory (LM) task and in the 3-back (3-B) transfer task. For illustrative purposes, the brain map shows the striatum (blue line) and pre-training activity for one single (young) subject. (b) The left striatum (peak -20 4 14) was activated before training and showed training-related increased activity for both letter memory and 3-back in younger adults. The dotted red lines indicate mean baseline BOLD values for the striatal region (mean of those trained before, controls before, and controls after). (c) The effect size for older trained participants was significantly higher compared to the controls in the trained letter memory (LM) task. (d) The left striatum (peak -24 10 -2) showed a training-related increase for letter memory in older adults. Error bars indicate standard errors around mean values.

On the basis of increased post-training activity in the striatum for both letter memory and 3-back, we conducted a conjunction analysis and assessed commonalities in between-session activation for these tasks. Finally, an additional conjunction analysis revealed that

the striatal region, showing training-related increases for both letter memory and 3-back, overlapped with the striatal region jointly activated at pre-training (Fig 5b).

For the elderly, significantly higher effect size was found for trained participants compared to controls in the trained letter memory task. Hence, trained participants improved more in performance from pre- to post-training compared to the control participants (Fig 5c). However, no significant transfer effects were found in performance. These behavioural findings indicate age-related neural constraints on updating learning and transfer, which was supported by the fMRI analyses. The striatum was not significantly activated during letter memory pre-training for the elderly, although they activated fronto-parietal regions. Analyses of training-related changes in brain activity revealed however increased activity in the left striatum for training participants' relative controls (Fig 5d), but no significant changes were found for the 3-back transfer task.

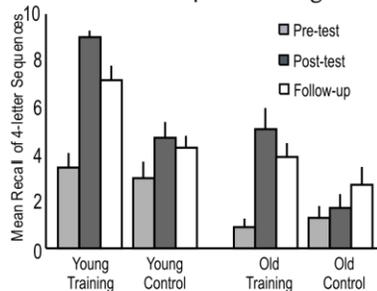
Study II

Dahlin, E., Nyberg, L., Bäckman, L. & Stigsdotter Neely, A. (2008). Plasticity of Executive Functioning in Young and Old Adults: Immediate Training Gains, Transfer, and Long-Term Maintenance, *Psychology and Aging*, 23(4), 720-730.

Among previous studies investigating training of working memory and executive functioning there are limited numbers that have investigated long-term maintenance (Table 2). No previous studies have investigated long-term maintenance following updating training per se, and only one has investigated follow-up effects of transfer (Li et al., 2008). In the current study we addressed the issue of the durability of training effects when reporting data from an 18-month follow-up session. Moreover, we reported behavioural data from a larger sample compared to Study I and used a broader battery of cognitive transfer tasks (see Table 4 for a description of the tasks included).

Analysis of training-related changes in performance revealed significant group by session interactions for both young and old

a. Performance Letter memory pre-, post- and 18 months post-training-



b. Individual differences in training-related gains

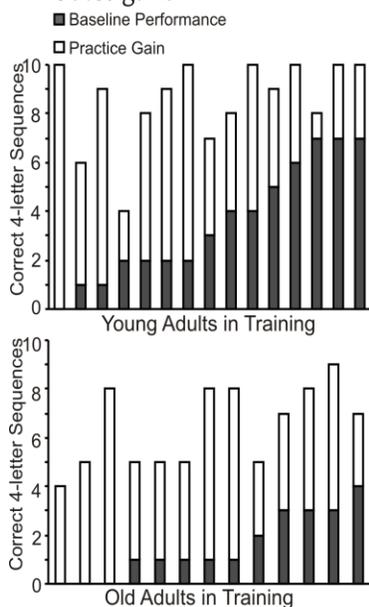


Figure 6. Letter memory performance in young and old participants pre-training, post-training and 18 months post-training. The training effect remained in both young and old participants 18 months post-training

participants, indicating that trained participants improved significantly more pre- to post-training compared to the controls for each particular age group (Fig 6a). In fact, results from the trained letter memory task revealed that all individuals improved in performance as a result of training (Fig 6b). An age comparison of performance in the tasks included during the five-week training period revealed no significant interaction in the four training tasks that required updating of single items (i.e., letters, numbers, colours, or spatial location, Fig 4a-d), which indicates that both age groups improved at a similar level. But an exception was the keep-track task (Fig 4e), in which younger but not older adults showed training-related gains.

Another issue investigated was whether training generalized to other transfer tasks. Analyses of transfer tasks listed in table 4 revealed a significant group by session interaction for the 3-back task (the same result as reported

in study I) and the recall of concrete nouns task in young subjects but not elderly subjects. Hence, the main outcome of the analyses of the transfer task was limited generalizability of updating training to other cognitive domains and the transfer effects found were restricted to young participants.

All trained older participants, and 11 of the 15 trained young participants, returned for follow-up testing 18 months post-training. All the drop-outs had moved from the community at the time for the follow-up. Seven young and seven elderly subjects from the control groups were invited back to participate. The remaining controls were not invited back due to practical reasons. Analyses of performance at the follow-up revealed that the training effect remained in both young and old participants 18 months post-training (Fig 6a). Moreover, the positive transfer effect to 3-back in the young subjects was maintained in the follow-up test.

Study III

Nyberg, L., Dahlin, E., Stigsdotter Neely, A. & Bäckman, L. (2009). Neural Correlates of Variable Working Memory Loads Across Adult Age and Skill: Dissociative Patterns within the Fronto-parietal Network, *Scandinavian Journal of Psychology*, 50(1), 41-46.

The neural bases for limitations in executive functioning have reached an increased interest in recent years. The findings from previous studies are however inconsistent since the dorsal prefrontal cortex has been correlated with both capacity-unconstrained responses (Braver et al., 1997; Linden et al., 2003) and capacity-constrained responses (Callicott et al., 1999), and the parietal cortex has been correlated with both capacity-unconstrained responses (Braver et al., 1997; Cohen et al., 1997) and capacity-constrained responses (Callicott et al., 1999; Linden et al., 2003). The inconsistent findings in previous studies motivated us to analyse the *n*-back task with regard to individual differences in executive differences in Study III. Findings from Study I and II suggest that *n*-back was sensitive to updating and the properties

of the task permit load manipulation, which made it possible to use the tasks for the investigation of mapping between executive load and regional brain activity. Of the young participants, a median split based on 3-back performance divided 11 into a low-performing group and 11 into a high-performing group. The 11 participants included in the older group were selected so that all participants performed below the level of all the individuals in the young-high performing group. Results revealed that in comparison to the young-high group, the older group showed signs of a decline in performance already between 1- and 2-back and the young-low performers showed a significant decline in performance between 2- and 3-back (Fig 7a).

The conjunction analysis aimed at identifying load-dependent brain regions identified regions in both fronto-parietal and sub-cortical areas such as the thalamus and the striatum (See Table 3 in Study III for peak values). Analyses aimed at identifying brain regions with differences between the three groups identified three brain regions with significant group differences. In a right inferior parietal area (Fig 7b), the capacity constraints were apparently already between load 1 and 2 for the older group and between 2 and 3 for both the older and the young-low performing group in this area. In a left pre-central frontal area (Fig 7c), young-high performing participants showed a capacity-unconstrained response, whereas the older group showed a decrease in activity with increasing load. For young-low performers a capacity constraint was seen between load 2 and load 3. Note that the old group showed a significantly greater activation than both young groups at the lowest load level. An interesting pattern of group differences was also found in the left thalamus (Fig 7d). This region showed a similar pattern as the parietal region, with a capacity-unconstrained pattern for young-high and a constraint at level 1 for old, and load 2 for young-low performers. A general effect of manipulation of executive demand was also observed in the striatum (right caudate nucleus), and a load-effect was observed for younger but not older performers in this region.

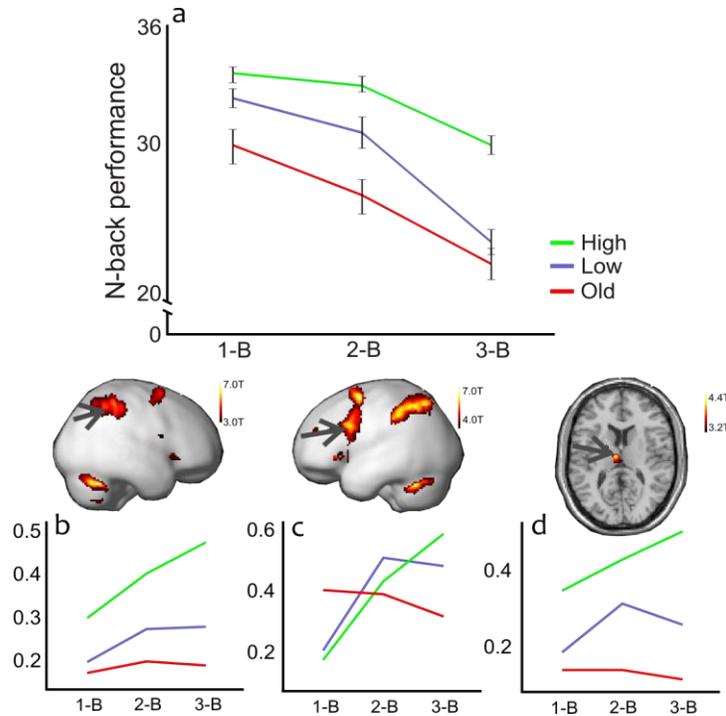


Figure 7. Load-sensitive activation patterns in fronto-parietal and sub-cortical areas. (a) All groups showed a decrease in the number of correct responses as a function of load. The magnitude of brain activity corresponded to the behavioural data in the (b) parietal cortex and the (d) thalamus at all three load levels with a magnification of group differences in magnitude as a function of load. The magnitude of activation in a dorsal frontal region (c) differed within capacity limitations so that old > young at 1-back and young-low > young-high at 2-back. The y-axis (b-d) represents % BOLD-signal change. Error bars represent standard errors around mean values.

GENERAL DISCUSSION

The purpose of this thesis was to increase knowledge of performance and brain activity changes in trained and transfer tasks following training of an isolated executive function: updating. Moreover, load-dependent differences in brain activity were investigated by analyses of three different groups performing the *n*-back task. The results

support previous findings that fronto-parietal and sub-cortical areas are crucial for individual differences in executive functioning. Further, the results revealed that it is possible to improve in performance on trained tasks for both young and old participants, and this effect was maintained 18 months post-training. Another central finding was that young participants improve in performance on an untrained updating task as well, and this transfer effect was maintained 18 months post-training. The main finding, with regard to neural correlates, was that the transfer effect was based on joint striatal activity for the trained and the transfer task. These findings will be discussed in relation to previous research below.

Improvement in performance following updating training

As can be seen from the literature review in the introduction, it is possible to reduce reaction times (Jansma et al., 2001) and increase performance following working memory training (Brehmer et al., 2008; Jaeggi et al., 2008; McNab & Klingberg, 2008; Olesen et al., 2004; Westerberg & Klingberg, 2007). It is also reported that it is possible to modify performance following dual-task (Bherer et al., 2005, 2008; Erickson et al., 2007) and task-shifting training (Gaab et al., 2006; Karbach & Kray, in press; Kramer et al., 1999; Minear & Shah, 2008). The training programme created for studies I and II was aimed at investigating training-related changes in performance and neural correlates. Training tasks were created for the purpose of activating a well-defined executive function, updating, and of activating brain areas underlying this function. Training of tasks involving the updating component has reported improved performance following training (Li et al., 2008; Jaeggi et al., 2008), but only one previous study has investigated updating per se. They report that it was possible to modify the updating process in young healthy subjects (Hempel et al., 2004). Hence, studies I and II are the firsts to include both young and old participants in training of updating per se, which makes age comparisons possible.

We found that both age groups improved in performance on almost all training tasks as a result of training, even if the elderly initially performed at a lower level compared to young participants (Study II). The pattern of cognitive plasticity in old age and age-related constraints in cognitive functioning characterizes much intervention research comparing individuals across the adult life span (Baltes & Kliegl, 1992; Jones et al., 2006; Verhaeghen, Marcoen, & Goossens, 1992). Both age groups improved at a similar level in the training tasks requiring updating of single items (i.e., letters, numbers, colours, or spatial location) but in the keep-track task younger, but not older adults showed training-related gains. This task required updating, categorization, and association and may be more cognitively complex compared to the four training tasks that only required updating. Previous studies have revealed that when tasks become more complex, the performance of the elderly degrades to a greater extent than that of young people (McDowd, 1986); hence the level of complexity in the training task may be important for the outcome, especially for the elderly. However, ceiling effects for the young make these findings difficult to interpret and more investigations are needed to draw firm conclusions. An age comparison of pre- and post-training performance in the letter memory criterion task revealed a significant interaction effect indicating a more pronounced training effect for the young compared to the old. However, for the present purposes, older adults did show substantial training-related gains, gains that in relative terms were comparable or even greater than those of the young adults.

Taken together, we found an enhanced performance following updating training in both young adults and the elderly.

Neural changes following updating training

Studies investigating training-related changes in brain activity have reported both fronto-parietal increases (Olesen et al., 2004; Westerberg & Klingberg, 2007) and decreases (Brehmer et al., 2008; Erickson et al., 2007; Jansma et al., 2001) following working memory and executive functioning training. It is not clear how to interpret such divergent training-related brain activity changes with respect to neural efficiency. Increases in activity may reflect recruitment of additional cortical units with practice, alternatively they may stem from a strengthening of the Blood Oxygenation Level Dependent (BOLD) response within a particular region (Poldrack, 2000).

Our analyses of training-related brain activity changes revealed fronto-parietal decreased activation in the trained task for the young. This is a common pattern after both repeated exposure to executive tasks (Chein & Schneider, 2005) and more extensive training (Kelly et al., 2006; Kelly & Garavan, 2005). More precisely, the decreased activation was located in the anterior prefrontal cortex (BA 10), the superior parietal cortex (BA7) and the supramarginal gyrus (BA 40), all areas important for higher order cognitive processing and attention modulation (Cabeza & Nyberg, 2000). As alluded to in the literature review in the introduction, superior parietal cortex has been associated with executive functioning in general, whereas anterior prefrontal cortex has been thought to be unique to updating (Collette et al., 2005; Wager & Smith, 2003), and especially critical in the updating of letters (Collette et al., 2007;). Hence, the pattern of decreased activation in these areas may indicate that the task was less executively demanding post-training when compared to pre-training, and especially the updating process had been more efficient.

In addition, we found increased activity in the striatum (Study I). The finding of training-related increases in sub-cortical areas such as the striatum are reported in studies investigating brain activity changes following working memory training (Dahlin et al., in press), and increases in sub-cortical areas may indicate changes in the underlying skill following training. The area where we found the

training-related increased activity was located in the associative striatum, which indicates that it was a cognitive process that had been influenced by the training. The striatum serves as the input centre for the basal ganglia and has been described as a gating mechanism responsible for deciding which processes need to be worked on by the frontal and parietal areas (O'Reilly, 2006). We suggest that the increased activity in the striatum, together with the decreased fronto-parietal activity following training (Study I), indicates that the process used to solve the trained task is more automatic post-training than it is pre-training. The brain circuits involved in task performance have shifted from a broader, dispersed network to a specific and more optimal circuit of neural regions that are functionally interconnected to mediate efficient updating.

We did not find any training-related decreased brain activity in the elderly, which may indicate that after training the task was still rather difficult for them. One proposal is that the task was initially too difficult for the elderly and the task-specific training should therefore increase the ability to keep the frontal cortex engaged after training. This suggestion is in line with findings in Study III reporting that greater frontal activity reflects a dynamic reallocation of resources to maintain high task performance when the task is executively demanding and the capacity is constrained. Further, an important determinant of executive limitations is the ability to keep the frontal cortex adequately engaged, and task-specific training should be expected to lead to reduced frontal activity if the task is already within capacity limits before training. However, there are findings indicating that brain activity changes are not constant during a training period. Four weeks of daily training on the *n*-back task revealed increased fronto-parietal activation initially, but more training leads to decreased activation (Hempel et al., 2004). It is impossible to know how brain activity changed during the training period in our study, and it is even more difficult to ascertain whether more training would have revealed a different outcome. However, my suggestion is that more training would have revealed a more automatic process and hence decreased fronto-parietal activity even in the elderly participants,

instead of the increased activity we found following 5 weeks of training.

Improvement on transfer tasks following updating training

Behavioural transfer effects

An important aspect of training interventions is finding transfer effects following training. Despite a significant effect in the trained task, the general pattern in studies investigating transfer effects is *limited* transfer effects (Dahlin et al., in press; Green & Bavelier, 2008). The general rule is that transfer effects are more common when trained and transfer tasks are similar to each other (see the introduction for the literature review), and in line with this assumption, we found transfer effects to two tasks for young participants despite a wide battery of transfer tasks included in study II. The transfer effects found were to an updating task (3-back) and an episodic memory task (recall of concrete nouns). The episodic memory task was administered so the participants had to keep track of items that had recently been presented, as well as items that were recalled on the last trial. This feature - to keep track of reminded and non-reminded items - may require an updating of memory representations and the operational overlap with the trained task was probably an explanation of the effect found in this specific task. However, the inconsistency of results when young trained subjects improved from pre-test to post-test and declined in the 18-month follow-up test, whereas the controls improved from post-test to follow-up test, would suggest that these data should be interpreted with caution. The transfer effect to the 3-back task was more stable and remained in the follow-up.

Even if we found transfer effects to tasks that taxed the trained executive function updating, several studies have to some extent shown that expectations based on similarities between the obvious surface elements can be incorrect. For example, it was found in an alphabet arithmetic task (e.g., $A + 2 = C$) that there was very little transfer of gains in performance following practice with one set of

stimuli to a second set of stimuli even if the elements were almost identical (Logan & Klapp, 1991). Hence, the question of *how* and *when* transfer effects appear are rather complex. The relation between trained and transfer tasks may be important, but the fact that researchers have not found any solution in the transfer question, despite years of investigations, motivates a search for the answer elsewhere. It is assumed that there is a neurological foundation that has evolved to support transfer (Haskell, 2001). Neuroscience has not played a role in the study of transfer although mental models and mental representations have. A relatively new theory of the neurological limitations of cognitive transfer based on precepts of evolutionary psychology and cognitive neuroscience argues that one possibility is that transfer could be limited to the evolution of the human brain (Atherton, 2007). Hence, they argue that one explanation for the common finding of limited transfer effects may be that the various areas of the brain are not fully connected to each other. Moreover, it has been hypothesized that overlapping networks or brain areas for the trained and the transfer tasks are necessary for producing transfer effects (Jonides, 2004) and knowledge about neural correlates of transfer may shed further light on underlying mechanisms.

Neural correlates in transfer tasks

With regard to the unity and diversity of executive functioning (Miyake et al., 2000) and with the hypothesis of overlapping brain regions in mind, it is interesting to highlight that we found fronto-parietal activation before training, not only for the trained updating task (letter memory) and the updating transfer task (*n*-back), but also for the inhibition transfer task (Stroop) for young adults. Hence, although a similar fronto-parietal cortical system was activated for all executive tasks examined, the transfer effect apparently required a specific processing component and associated brain systems. The hypothesis that a basis for transfer is that training and transfer tasks recruit overlapping neural systems (Jonides, 2004) may thus be too general.

In study 1, we reported selective overlapping activity in the striatum before training in the trained letter memory task and n -back transfer tasks, which is interesting in relation to the behavioural finding of transfer effects to the n -back task in young participants. No striatal overlap was found in the Stroop task of inhibition, which is consistent with the lack of behavioural transfer to this task. Moreover, we found overlapping training-related increases for both letter memory and n -back in the associative striatum and we suggest that the striatal complex was a key component in mediating transfer effects after training on updating. Studies have proposed that the striatum is a gating structure selecting specific regions in the frontal cortex to be updated or to maintain already existing information (O'Reilly, 2006), and the increased activity can be proposed to indicate a more effective updating skill post-training.

Altogether, the suggestion is that there are task-specific regions important for mediating transfer effects, and our findings revealed a critical role for the striatum in mediating transfer effects after updating training. With regard to the foregoing review of neural correlates in executive functioning, transfer effects should be more common if a more general fronto-parietal system were underlying transfer effects. The finding that a specific striatal system mediates transfer effects is hence in agreement with previous findings of limited transfer effects (Table 2). However, other forms of training will likely depend on other brain regions and I hope this question will be elaborated further in future research. Even though the conclusion is based on a limited regime of tasks, the observed selectively in the neural basis of transfer is consistent with numerous behavioural findings of limited transfer effects.

Long-term maintenance following updating training

Only a few previous studies have investigated long-term maintenance following training in young adults and older participants. In the elderly, it has been found that everyday functional outcomes can be

maintained as long as 5 years post-training (Willis et al., 2006) and encoding and retrieval skills can be maintained at least 3.5 years post-training (Stigsdotter Neely & Bäckman, 1993). Another study investigating a brain plasticity-based training programme with working memory tasks found maintenance effects 3 months post-training in the elderly (Mahncke et al., 2006). Together, these studies have shown that the abilities trained can be maintained over years.

Despite the relevance of durability of training, this factor has not been well studied after working memory and executive functioning training, and there are only a few studies that have highlighted this topic in young adults (Dahlin et al., in press). The two studies investigating long-term maintenance listed in Table 2 report maintenance of training performance in both young adults and the elderly 2 months post task-shifting training (Kramer et al., 1999) and maintenance effects of both training and transfer effects 3 months post-training in young adults and the elderly, although the elderly did not maintain their performance as well as younger subjects (Li et al., 2008).

No previous study has investigated long-term maintenance following training of updating per se, and one of the main topics in study II was therefore the investigation of durability. We found maintenance effects as long as 18 months post-training in both young adults and the elderly. Moreover, the transfer effect found in the young was also maintained in the follow-up test, which indicates a rather robust influence of updating training. The finding of long-term maintenance is of high relevance because without information on maintenance effects and effects on transfer tasks, it is difficult to discern whether intervention effects are restricted to the formation of a new skill, with little consequences for behaviour unrelated to this skill, or whether cognitive mechanisms and capacities of general applicability have been enhanced.

Individual differences in executive functioning

Differences between young and old participants in updating performance, training-related changes, transfer, and brain activity are frequently reported in Study I, II and III, which indicates that there are individual differences in updating and executive functioning. A previous study has reported that individual differences in updating can influence several everyday activities, such as the ability to solve arithmetic problems (Passolunghi & Pazzaglia, 2004), which motivates further discussions on individual differences in executive functioning.

Individual differences in relation to training data

Frequently reported in this thesis are differences in updating performance between young and old participants. These differences can most probably be explained by evidence that executive functions are negatively affected in later adulthood (Kray & Lindenberger, 2000; Salthouse & Babcock, 1991; Van der Linden & Bredart, 1994). However, even if the elderly performed below young subjects, the positive effects of updating training were underscored by the fact that older participants performed above the initial baseline performance level for young adults on the letter memory criterion task post-training. Hence, the elderly performed as if they were 40 years younger following five weeks of updating training per se. This finding may indicate that it is possible to decrease group differences in updating performance by giving updating training to the executive weaker group. The finding is however inconsistent with a previous finding that maximum performance of older adults after 45 days of training on spatial shifting and updating was still lower than that of younger adults (Li et al., 2008).

Another interesting finding to be highlighted is that all participants showed improvements in performance on the trained updating task (Study II). There were, however, large individual differences in how much they improved from pre- to post-training and further investigations of these differences should be interesting. Whether long-term maintenance was influenced by individual

differences in executive functioning have been investigated (unpublished data) but no significant correlations between executive performance and long-term maintenance were found. Individual differences can however influence the degree of transfer after training (Sohn et al., 2006). Therefore, the lack of transfer effects found at group level in the elderly motivated further investigation of individual differences in older subjects. Manual inspections of the data revealed that some of the older subjects improved more in the 3-back transfer task compared to the others. No significant differences between these individuals and the remaining ones were found pre-training, but the sub-group increased significantly more pre- to post-training in the 3-back task (unpublished data) compared to others. Hence, even if we did not find significant transfer effects at a group level in Study I and II, at least some individuals in the older group may generalize the training to the 3-back transfer task. Analyses of background characteristics did not reveal significant differences between this sub-group and the remaining older subjects in respect to years of education, depression, verbal ability, mental status, attention or mental speed functions. The mean age was 67.67 (range 66-71) and hence, age could not be a distinguishing factor. Therefore, we were searching for the answer somewhere else, and when comparing striatal activity for these subjects we found training-related increases in brain activity in line with the findings in the young following training (Fig 8). This finding further underscored the striatum as a core region underlying transfer effects following updating training and indicates that there are individual differences in the possibilities to modify the fronto-striatal network in the elderly. There are elderly subjects who resemble the young ones and the finding is in line with evidence showing that individual differences in cognitive ability can influence the degree of transfer after training (Sohn et al., 2006).

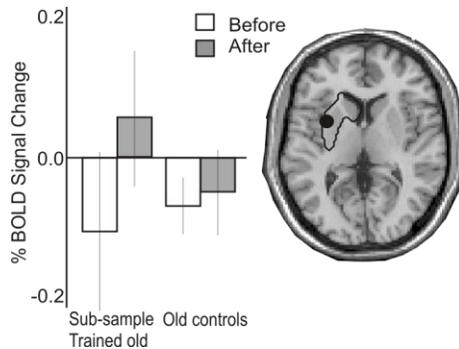


Figure 8. A sub-sample of older trained adults improved in the 3-back task even if no transfer effects were found at group level (Studies I and II). This change in performance was mediated by striatal increases (Peak -30 4 6; black dot in brain template) for this sub-sample in comparison to older controls. This finding is in agreement with findings in Study I that striatal activity mediates transfer effects in young adults and indicates that the fronto-striatal network can be modified even in older adults. The striatum is marked with a black line in the brain template.

Individual differences in relation to brain mapping

Even if the neural basis for limitations in executive functioning have been a subject of increased interest in recent years, the mapping between individual differences in executive functioning and regional brain activity is still an unresolved issue. Previous studies have revealed that the dorsal prefrontal cortex has been correlated with both capacity-unconstrained responses (Braver et al., 1997; Linden et al., 2003) and capacity-constrained responses (Callicott et al., 1999). Also the parietal cortex has been correlated with both capacity-unconstrained responses (Braver et al., 1997; Cohen et al., 1997) and capacity-constrained responses (Callicott et al., 1999; Linden et al., 2003). The findings described above are somehow conflicting and to further complicate matters, a recent study reported that the mapping function between load and brain activity differs between young and old adults (Mattay et al., 2006). Specifically in the dorsal frontal cortex, old adults showed greater activation than younger adults at low load. At higher load the pattern was reversed due to a monotonic decreasing trend for the older along with an opposite tendency for the younger.

Findings from studies I and II indicate that the n -back task was sensitive to updating and moreover, the task design enables load manipulation. Therefore, we analysed individual differences in

executive load by comparing a low-performing young group, a high performing young group, and an elderly group of participants in Study III. The behavioural data confirmed that the load manipulation was effective in inducing capacity constraints, and the load, where the capacity was heavily taxed, differed across groups.

The findings of brain activity show that the magnitude of activity corresponded to the behavioural data with a magnification of group differences in magnitude as a function of load in the parietal cortex and thalamus at all three load levels. The findings are in agreement with previous proposals that the parietal cortex is a key neural locus of capacity limitations (Todd & Marois, 2004), and the capacity-constrained response in the thalamus is also in keeping with previous observations (Callicott et al., 1999). The activation pattern in the dorsal frontal region also adhered to a capacity-constrained response function. However, there was a critical difference in the activation magnitude between the frontal response pattern and that seen in the parietal cortex and thalamus. The magnitude of activation differed within limitations in executive functioning such as old > young at 1-back and young-low > young-high at 2-back. This finding is consistent with previous research (Mattay et al., 2006) and indicates that greater frontal activity may reflect dynamic reallocation of resources to maintain task performance. An indication for a compensatory response can also be seen in young-low performers; they showed greater frontal activation at load 2 compared to young-high performers (Fig 7c). However, this difference failed to reach significance. A general load-effect was also found in the striatum for the younger but not for the elderly, and the differences between the young groups may be explained in terms of variability in the effectiveness of fronto-striatal control over encoding and/or updating (O'Reilly, 2006) in working memory. Findings from Study I demonstrate a more effective fronto-striatal network after training and hence I suggest that individual differences can be minimized by providing training on updating to the low-performing group. Additional changes in the older group could reflect age-related changes in basal ganglia regions (Buckner, 2004). With regard to the

main finding in study I, that the selective transfer effect was based on activity in the striatum, these age-related changes may also explain the lack of transfer effects found in the elderly.

Is it possible to generalize the outcome for other groups of participants?

In relation to individual differences, it is interesting to pose the question of whether it is possible to generalize the outcome from studies I and II to other groups of participants e.g., patients with cognitive decline. The training regimen described in studies I and II has so far also been used in two additional studies including two different patient groups with cognitive deficits. Preliminary results from these studies have revealed positive training effects in both children with special educational needs (Jonsson, Nyberg, Jonsson, & Stigsdotter Neely, 2008) and burn-out patients (Aronsson, 2009).

In the study including children with special educational needs, participants trained in four of the computer tasks used in the training described in this thesis (Fig 4 a, c, d, e). Training was given during a period of five weeks with five sessions per week (approximately 20 min/session). All participants improved from pre- to post-test, but the trained group improved more compared to the controls in all training tasks. Between group differences in gain were also found for transfer tasks critical for reading and reasoning but a significant transfer effect was only found in a number memory transfer task (Fig 4b; Jonsson et al., 2008).

In the study including burn-out patients, thirteen women between 34 to 61 years old were included. Seven participants received training on a training programme, identical to the one described in this thesis, for five weeks with three sessions per week. Results revealed that trained participants improved more in performance compared to untrained participants in the trained task. The training group improved in performance in the 3-back transfer task to the same degree as the young in study II, whereas the controls did not change in performance even though no significant transfer effects were reached (Aronsson, 2009).

With these two additional studies in mind it may be possible to generalize the training results found in studies I and II for other groups of participants, at least on a behavioural level. Measurement of brain activity was not included, and therefore it is difficult to draw firm conclusions about the possibilities of generalizing our outcomes on a neural level. A study including brain activity measurements following the training regimen used in studies I and II in Parkinson patients is however planned and these results will be interesting.

Limitations and future directions

I think some possible limitations of this thesis should be mentioned. A first limitation is that the number of participants in each group was relatively low. Other studies investigating behavioural measurements after training often include at least 30 in each group (Jaeggi et al., 2008; Minear & Shah, 2008; Sohn et al., 2006). However, as alluded to above, our positive findings of updating training have been replicated in both children with special education needs (Jonsson et al., 2008) and burn-out patients (Aronsson, 2009). Moreover, the finding of limited transfer effects to 3-back has also been replicated in a student project (unpublished), and therefore I am confident with the findings despite the low numbers of participants included.

A second limitation is that we have only discussed transfer effects to experimental tasks. Outcome on everyday performance is an often neglected aspect of cognitive training interventions (Chaytor & Schmitter-Edgecombe, 2003) and not unique to our study. However, we have asked the participants whether they had experienced any effects on everyday performance following training and if so, in which everyday situations or tasks they experienced improved functioning. These data showed that none of the participants in the control groups experienced effects on everyday performance, whereas 85% of the older trained adults and 40 % of the younger trained adults did (Dahlin, Nyberg, Sandberg, Bäckman, & Stigsdotter Neely, 2007). The most common areas of reported improvements were related to being

better at remembering planned things to do, like buying a particular item in the store or doing something in a few minutes, such as turning off the stove and reading a text with less attentional slips, compared to before training. It is encouraging to note that the types of everyday situations where positive change was experienced were predominately related to prospective memory and to attention, both cognitive domains closely related to executive functioning.

A third limitation is that we cannot measure neural transmitters as dopamine with fMRI. Positron emission tomography (PET) is a nuclear imaging technique that can measure density of neurotransmitters as dopamine in the brain and PET studies have revealed that striatal and extrastriatal dopamine activities can be modulated during executive task processing (Aalto, Bruck, Laine, Nagren, & Rinne, 2005; Monchi, Ko, & Strafella, 2006). The striatal dopamine system has also been described as a powerful mediator of age-related differences in executive functioning (Erixon-Lindroth et al., 2005). Dopamine measurements should hence be fascinating here with regard to one of the main findings of the importance of the fronto-striatal network.

Despite the importance of dopamine in relation to the studies included in this thesis, this topic is not investigated further here. The intention was to include a fourth paper taxing this issue, but unpredictable course of events made this impossible. The aim of the fourth paper was to investigate whether the training-related increased striatal activity (measured with fMRI) found in study I reflected an increased dopamine release.

D2 receptors are common in the striatum and our intention was to use ^{11}C -raclopride PET to investigate the D2 uptake during the letter memory task performance before and after five weeks of updating training. Preliminary results from 8 young healthy individuals reveal that the binding potential in the caudate nucleus decreased during the active task pre-training, which indicates that performance of the letter memory task increases the release of dopamine into the striatum. This is an ongoing study and it is still unclear whether the

increased striatal activation we found in study I indicates an increased dopamine release following training.

CONCLUDING REMARKS

The studies included in this thesis were the first to investigate brain activity, training, transfer and long-term maintenance following training of an isolated executive function - updating - in both young and old participants. The *n*-back was sensitive to updating and the task design enabled load manipulation, which also made it possible to analyse brain activity related to individual differences and executive functioning. I have presented ideas of how updating training affects both the brain and behaviour. These ideas are based on well controlled empirical studies and I am therefore confident when saying that it is possible to improve performance in trained updating tasks in both young and old healthy adults. The effects can also be maintained at least 18 months post-training. In line with previous studies, transfer effects in general were difficult to find, and restricted to young participants. The transfer effect found was however maintained over time, which was revealed in the follow-up test. Moreover, we found that the fronto-striatal control over updating was more effective post-training for young participants, and striatal overlapping activity in the trained and transfer task was central for the behavioural transfer effects found. Study III supports and extends previous findings of how brain activity in the frontal, parietal and sub-cortical regions is influenced by executive demand and individual differences in capacity. Individual differences between the young groups could be explained in terms of variability in the effectiveness of fronto-striatal control over updating, and my suggestion is that individual differences may be reduced by providing updating training to groups with limited executive functioning. Together, the findings show that the underlying updating skill was strengthened following training and not only task performance per se. The work presented here has revealed several novel findings as well as indicating important directions for the future.

REFERENCES

- Aalto, S., Bruck, A., Laine, M., Nagren, K., & Rinne, J. O. (2005). Frontal and temporal dopamine release during working memory and attention tasks in healthy humans: A positron emission tomography study using the high-affinity dopamine D2 receptor ligand [¹¹C]FLB 457. *J Neurosci*, *25*(10), 2471-2477.
- Adcock, R. A., Thangavel, A., Whitfield-Gabrieli, S., Knutson, B., & Gabrieli, J. D. E. (2006). Reward-motivated learning: Mesolimbic activation precedes memory formation. *Neuron*, *50*(3), 507-517.
- Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Ann Rev Neurosci*, *9*(1), 357-381.
- Aronsson, I. (2009). *Träning av den exekutive förmågan uppdatering hos personer med stressrelaterade besvär*. Master's Thesis, Umeå University, Sweden.
- Atherton, M. (2007). *A Proposed Theory of the Neurological Limitations of Cognitive Transfer*. Paper presented at the April 2007 annual meeting of the American Educational Research Association, Chicago, IL.
- Baddeley, A. D. (1996). Exploring the central executive. *Q J Exp Psychol-A*, *49*(1), 5-28.
- Baddeley, A. D. (1986). *Working memory*. Oxford: Clarendon Press.
- Baltes, P. B., & Kliegl, R. (1992). Further testing of limits of cognitive plasticity: Negative age differences in a mnemonic skill are robust. *Dev Psychol*, *28*(1), 121-125.
- Beck, A. T., & Steer, R. A. (1996). *Beck Depression Inventory: Manual* (Swedish version). Stockholm: Psykologiförlaget AB.
- Bherer, L., Kramer, A. F., Peterson, M. S., Colcombe, S., Erickson, K., & Bécic, E. (2005). Training effects on dual-task performance: Are there age-related differences in plasticity of attentional control? *Psychol Aging*, *20*(4), 695-709.

- Bherer, L., Kramer, A. F., Peterson, M. S., Colcombe, S., Erickson, K., & Becic, E. (2008). Transfer effects in task-set cost and dual-task cost after dual-task training in older and younger adults: further evidence for cognitive plasticity in attentional control in late adulthood. *Exp aging res*, *34*(3), 188 - 219.
- Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E., & Noll, D. C. (1997). A parametric study of prefrontal cortex involvement in human working memory. *NeuroImage*, *5*(1), 49-62.
- Brehmer, Y., Westerberg, H., Rieckmann, A., Fischer, H., & Bäckman, L. (2008). *Neural Correlates of Working Memory Training in Younger and older Adults: An fMRI Study*. Poster presented at the Cognitive Aging Conference, Atlanta, GA.
- Buckner, R. L. (2004). Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. *Neuron*, *44*(1), 195-208.
- Burgess, P. W., & Shallice, T. (1996). Response suppression, initiation and strategy use following frontal lobe lesions. *Neuropsychologia*, *34*(4), 263-272.
- Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J Cognitive Neurosci*, *12*(1), 1-47.
- Callicott, J. H., Mattay, V. S., Bertolino, A., Finn, K., Coppola, R., Frank, J. A., et al. (1999). Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cereb Cortex* *9* (1), 20-26.
- Cervenka, S., Bäckman, L., Cselényi, Z., Halldin, C., & Farde, L. (2008). Associations between dopamine D2-receptor binding and cognitive performance indicate functional compartmentalization of the human striatum. *NeuroImage*, *40*(3), 1287-1295.
- Chaytor, N., & Schmitter-Edgecombe, M. (2003). The ecological validity of neuropsychological tests: A review of the literature on everyday cognitive skills. *Neuropsychol R*, *13*(4), 181-197.

- Chein, J. M., & Schneider, W. (2005). Neuroimaging studies of practice-related change: fMRI and meta-analytic evidence of a domain-general control network for learning. *Cogn Brain Res*, *25*(3), 607-623.
- Cohen, J. D., Perlstein, W. M., Braver, T. S., Nystrom, L. E., Noll, D. C., Jonides, J., et al. (1997). Temporal dynamics of brain activation during a working memory task. *Nature*, *386*(6625), 604-608.
- Collette, F., Hogge, M., Salmon, E., & Van der Linden, M. (2006). Exploration of the neural substrates of executive functioning by functional neuroimaging. *Neuroscience*, *139*(1), 209-221.
- Collette, F., & Van der Linden, M. (2002). Brain imaging of the central executive component of working memory. *Neurosci Biobehav R*, *26*(2), 105-125.
- Collette, F., Van der Linden, M., Laureys, S., Arigoni, F., Delfiore, G., Degueldre, C., et al. (2007). Mapping the updating process: common and specific brain activations across different versions of the running span task. *Cortex*, *43*(1), 146-158.
- Collette, F., Van der Linden, M., Laureys, S., Delfiore, G., Degueldre, C., Luxen, A., et al. (2005). Exploring the unity and diversity of the neural substrates of executive functioning. *Hum brain mapp*, *25*(4), 409-423.
- Dahlin, E., Bäckman, L., Stigdotter Neely, A., & Nyberg, L. (in press). Training of the executive component of working memory: Subcortical areas mediate transfer effects. *Restor Neurol Neuros*.
- Dahlin, E., Nyberg, L., Sandberg, P., Bäckman, L., & Stigdotter Neely, A. (2007). *Long-term effects after executive training in elderly people*. Poster presented at the 9th Nordic Meeting in Neuropsychology. Gothenburg, Sweden.
- Dureman, I., & Sälde, H. (1959). *Psykometriska och experimentall-psykologiska metoder för klinisk tillämpning* [Psychometric and experimental-psychological methods for clinical application]. Uppsala, Sweden: Almqvist & Wiksell.

- Dyckman, K. A., Camchong, J., Clementz, B. A., & McDowell, J. E. (2007). An effect of context on saccade-related behavior and brain activity. *NeuroImage*, *36*(3), 774-784.
- Erickson, K. I., Colcombe, S. J., Wadhwa, R., Bherer, L., Peterson, M. S., Scalf, P. E., et al. (2007). Training-induced functional activation changes in dual-task processing: An fMRI study. *Cereb Cortex*, *17*(1), 192-204.
- Erixon-Lindroth, N., Farde, L., Robins Wahlin, T.-B., Sovago, J., Halldin, C., & Backman, L. (2005). The role of the striatal dopamine transporter in cognitive aging. *Psychiat Res Neuroim*, *138*(1), 1-12.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res*, *12*(3), 189-198.
- Frackowiak, R. S. J., Friston, K. J., Frith, C. D., Dolan, R. J., & Mazziotta, J. C. (1997). *Human brain function*. New York: Academic Press.
- Friedman, N. P., Miyake, A., Corley, R. P., Young, S. E., DeFries, J. C., & Hewitt, J. K. (2006). Not all executive functions are related to intelligence. *Psychol Sci*, *17*(2), 172-179.
- Gaab, N., Gaser, C., & Schlaug, G. (2006). Improvement-related functional plasticity following pitch memory training. *NeuroImage*, *31*(1), 255-263.
- Gazzaniga, M. S., Ivry, R. B., & Mangun, G. R. (2002). *Cognitive Neuroscience - The biology of the mind* (2nd ed.). New York: W. W. Norton.
- Green, C. S., & Bavelier, D. (2008). Exercising your brain: A review of human brain plasticity and training-induced learning. *Psychol Aging*, *23*(4), 692-701.
- Haskell, R. E. (2001). *Transfer of Learning - Cognition, Instruction, and Reasoning*. San Diego, CA: Academic press.
- Hempel, A., Giesel, F. L., Garcia Caraballo, N. M., Amann, M., Meyer, H., Wustenberg, T., et al. (2004). Plasticity of cortical activation related to working memory during training. *Am J Psychiatry*, *161*(4), 745-747.

- Huettel, S. A., Song, A. W., & McCarthy, G. (2004). *Functional Magnetic Resonance Imaging*. Sunderland, USA: Sinauer Associates Inc.
- Jaeggi, S. M., Buschkuhl, M., Jonides, J., & Perrig, W. J. (2008). Improving fluid intelligence with training on working memory. *PNAS*, *105*(19), 6829-6833.
- Jansma, J. M., Ramsey, N. F., Slagter, H. A., & Kahn, R. S. (2001). Functional anatomical correlates of controlled and automatic processing. *J Cogn Neurosci*, *13*(6), 730-743.
- Jones, S., Nyberg, L., Sandblom, J., Stigsdotter Neely, A., Ingvar, M., Petersson, K. M., et al. (2006). Cognitive and neural plasticity in aging: General and task-specific limitations. *Neurosci Biobehav R*, *30*(6), 864-871.
- Jonides, J. (2004). How does practice make perfect? *Nat Neurosci*, *7*(1), 10-11.
- Jonides, J., Schumacher, E. H., Smith, E. E., Lauber, E. J., Awh, E., Minoshima, S., et al. (1997). Verbal working memory load affects regional brain activation as measured by PET. *J Cogn Neurosci*, *9*(4), 462-475.
- Jonsson, B., Nyberg, L., Jonsson, K., & Stigsdotter Neely, A. (2008). *Working memory training in children with special education needs: A pilot study*. Poster presented at the 3rd annual meeting of the Nordic Center of Excellence in Cognitive Control, Reykavik, Iceland.
- Karbach, J., & Kray, J. (in press). How useful is executive control training? Age differences in near and far transfer of task-switching training. *Developmental Science*.
- Kelly, C., Foxe, J. J., & Garavan, H. (2006). Patterns of normal human brain plasticity after practice and their implications for neurorehabilitation. *Arch Phys Med Rehabil*, *87*(2), 20-29.
- Kelly, C., & Garavan, H. (2005). Human functional neuroimaging of brain changes associated with practice. *Cereb Cortex*, *15*(8), 1089-1102.

- Klingberg, T., Fernell, E., Olesen, P. J., Johnson, M., Gustafsson, P., Dahlström, K., et al. (2005). Computerized training of working memory in children with ADHD—A randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry* 44(2), 177-186.
- Klingberg, T., Forssberg, H., & Westerberg, H. (2002). Training of working memory in children with ADHD. *J Clin Exp Neuropsychol*, 24(6), 781-791.
- Kramer, A. F., Hahn, S., & Gopher, D. (1999). Task coordination and aging: Explorations of executive control processes in the task switching paradigm. *Acta Psychol*, 101(2-3), 339-378.
- Kramer, J. H., Reed, B. R., Mungas, D., Weiner, M. W., & Chui, H. C. (2002). Executive dysfunction in subcortical ischaemic vascular disease. *J Neurol Neurosurg Ps* 72(2), 217-220.
- Kray, J., & Epplinger, B. (2006). Effects of associative learning on age differences in task-set switching. *Acta Psychol*, 123(3), 187-203.
- Kray, J., & Lindenberger, U. (2000). Adult age differences in task switching. *Psychol Aging*, 15(1), 126-147.
- Li, S.-C., Schmirdek, F., Huxhold, O., Röcke, C., Smith, J., & Lindenberger, U. (2008). Working memory plasticity in old age: Practice gain, transfer, and maintenance. *Psychol Aging*, 23(4), 731-742.
- Linden, D. E. J., Bittner, R. A., Muckli, L., Waltz, J. A., Kriegeskorte, N., Goebel, R., et al. (2003). Cortical capacity constraints for visual working memory: Dissociation of fMRI load effects in a fronto-parietal network. *NeuroImage*, 20(3), 1518-1530.
- Logan, G. D., & Klapp, S. T. (1991). Automatizing alphabet arithmetic: I. Is extended practice necessary to produce automaticity? *J Exp Psychol Learn*, 17(2), 179-195.
- López-Luengo, B., & Vázquez, C. (2003). Effects of attention process training on cognitive functioning of schizophrenic patients. *Psychiat Res*, 119(1-2), 41-53.
- Luria, A. R. (1966). *Higher cortical functions in man*: London: Tavistock.
- Luria, A. R. (Ed.). (1979). *The making of mind: A personal account of soviet psychology*. In Cole, M. & Cole, S. (eds.), Cambridge: Harvard University Press.

- Mahncke, H. W., Connor, B. B., Appelman, J., Ahsanuddin, O. N., Hardy, J. L., Wood, R. A., et al. (2006). Memory enhancement in healthy older adults using a brain plasticity-based training program: A randomized, controlled study. *PNAS*, *103*(33), 12523-12528.
- Marklund, P., Larsson, A., Elgh, E., Linder, J., Åström Riklund, K., Forsgren, L., et al. (2009). Temporal dynamics of basal ganglia under recruitment in Parkinson's disease: transient caudate abnormalities during updating of working memory. *Brain*, *132*(2), 336-346.
- Martinez, D., Slifstein, M., Broft, A., Mawlawi, O., Hwang, D.-R., Huang, Y., et al. (2003). Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: Amphetamine-induced dopamine release in the functional subdivisions of the striatum. *Cereb Blood Flow Metab*, *23*(3), 285-300.
- Mateer, C. A. (1999). The rehabilitation of executive disorders. In D. Stuss, G. Winocur & I. Robertson (Eds.), *Cognitive Neurorehabilitation* (pp. 314-332). Cambridge, UK: Cambridge University Press.
- Mattay, V. S., Fera, F., Tessitore, A., Hariri, A. R., Berman, K. F., Das, S., et al. (2006). Neurophysiological correlates of age-related changes in working memory capacity. *Neurosci Lett*, *392*(1-2), 32-37.
- McDowd, J. M. (1986). The effects of age and extended practice on divided attention performance. *J Gerontol*, *41*(6), 764-769.
- McNab, F., & Klingberg, T. (2008). Prefrontal cortex and basal ganglia control access to working memory. *Nat Neurosci*, *11*(1), 103-107.
- Minear, M., & Shah, P. (2008). Training and transfer effects in task switching. *Mem cognition*, *36*(8), 1470-1483.
- Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cog Psychol*, *41*(1), 49-100.

- Monchi, O., Ko, J. H., & Strafella, A. P. (2006). Striatal dopamine release during performance of executive functions: A [¹¹C] raclopride PET study. *NeuroImage*, *33*(3), 907-912.
- Nichols, T., Brett, M., Andersson, J., Wagner, T., & Poline, J.-B. (2005). Valid conjunction inference with the minimum statistic. *NeuroImage* *25*(3), 653-660.
- O'Reilly, R. (2006). Biologically based computational models of high-level cognition. *Science*, *314*(5796), 91-94.
- Olesen, P. J., Westerberg, H., & Klingberg, T. (2004). Increased prefrontal and parietal activity post-training of working memory. *Nat Neurosci*, *7*(1), 75-79.
- Osaka, M., Osaka, N., Kondo, H., Morishita, M., Fukuyama, H., Aso, T., et al. (2003). The neural basis of individual differences in working memory capacity: an fMRI study. *NeuroImage*, *18*(3), 789-797.
- Osaka, N., Osaka, M., Kondo, H., Morishita, M., Fukuyama, H., & Shibasaki, H. (2004). The neural basis of executive function in working memory: an fMRI study based on individual differences. *NeuroImage*, *21*(2), 623-631.
- Owen, A. M., Downes, J. J., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia*, *28*(10), 1021-1034.
- Passolunghi, M. C., & Pazzaglia, F. (2004). Individual differences in memory updating in relation to arithmetic problem solving. *Learn individ differ*, *14*(4), 219-230.
- Poldrack, R. A. (2000). Imaging brain plasticity: Conceptual and methodological issues - a theoretical review. *Neuroimage*, *12*(1), 1-13.
- Posner, M., & Petersen, S. (1990). The attention system of the human brain. *Annu Rev Neurosci*, *13*(1), 25-42.
- Rasmusson, D. X., Rebok, G. W., Bylsma, F. W., & Brandt, J. (1999). Effects of three types of memory training in normal elderly. *Aging Neuropsychol C*, *6*(1), 56-66.

- Rogers, R. D., & Monsell, S. (1995). Costs of a predictable switch between simple cognitive tasks *J exp psychol gen*, *124*(2), 207-231.
- Salmon, E., Van der Linden, M., Collette, F., Delfiore, G., Maquet, P., Degueldre, C., et al. (1996). Regional brain activity during working memory tasks. *Brain Res*, *119*(5), 1617-1625.
- Salthouse, T. A., & Babcock, R. L. (1991). Decomposing adult age differences in working memory. *Dev Psychol*, *27*(5), 763-776.
- Schumacher, E. H., Lauber, E. J., Awh, E., Jonides, J., Smith, E. E., & Koeppe, R. A. (1996). PET evidence for an amodal verbal working memory system. *Neuroimage*, *3*(2), 79-88.
- Shimamura, A. P. (2000). The role of prefrontal cortex in dynamic filtering. *Psychobiology*, *28*(2), 207-218.
- Smith, E., & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science*, *283*(5408), 1657-1661.
- Smith, E. E., Jonides, J., & Koeppe, R. A. (1996). Dissociating verbal and spatial working memory using PET. *Cereb Cortex*, *6*(1), 11-20.
- Sohn, Y. W., Doane, S. M., & Garrison, T. (2006). The impact of individual differences and learning context on strategic skill acquisition and transfer. *Learn Individ Differ*, *16*(1), 13-30.
- Stigsdotter Neely, A., & Bäckman, L. (1993). Long-term maintenance of gains from memory training in older adults: two 31/2 year follow-up studies. *J Geront*, *48*(5), 233-237.
- Stoet, G., & Snyder, L. H. (2009). Neural correlates of executive control functions in the monkey. *Trends Cogn Neurosci*, *13*(5), 228-234.
- Tan, H.-Y., Chen, Q., Goldberg, T. E., S., M. V., Meyer-Lindenberg, A., Weinberger, D. R., et al. (2007). Catechol-O-Methyltransferase Val158Met modulation of prefrontal–parietal–striatal brain systems during arithmetic and temporal transformations in working memory. *J Neurosci*, *27*(49), 13393-13401.
- Thorndike, E. L., & Woodworth, R. S. (1901). The influence of improvement in one mental function upon the efficiency of other functions. *Psychol Rev*, *8*(3), 247-261.

- Tinaz, S., Schendan, H. E., Schon, K., & Stern, C. E. (2006). Evidence for the importance of basal ganglia output nuclei in semantic event sequencing: An fMRI study. *Brain Research, 1067*(1), 239-249.
- Todd, J. J., & Marois, P. (2004). Capacity limit of visual short-term memory in human posterior parietal cortex. *Nature, 428*(6976), 751-754.
- Tunik, E., Houk, J. C., & Grafton, S. T. (2009). Basal ganglia contribution to the initiation of corrective submovements. *Neuroimage, 47*(4), 1757-1766.
- Van der Linden, M., & Bredart, S. (1994). Age-related differences in updating working memory. *Brit J Psychol, 85*(1), 145.
- Van der Linden, M., Collette, F., Salmon, E., Delfiore, G., Degueldre, C., Luxen, A., et al. (1999). The neural correlates of updating of information in verbal working memory. *Memory, 7*(5-6), 549-560.
- Verhaeghen, P., Marcoen, A., & Goossens, L. (1992). Improving memory performance in the aged through mnemonic training: A meta-analytic study. *Psychol Aging, 7*(2), 242-251.
- Vogel, E. K., McCollough, A. W., & Machizawa, M. G. (2005). Neural measures reveal individual differences in controlling access to working memory. *Nature, 438*(7067), 500-503.
- Wager, T. D., & Smith, E. E. (2003). Neuroimaging studies of working memory: A meta-analysis. *Cogn Affect Behav Neurosci, 3*(4), 255-274.
- Westerberg, H., Jacobaeus, H., Hirvikoski, T., Clevberger, P., Stensson, M. L., Bartfai, A., et al. (2007). Computerized working memory training after stroke: A pilot study. *Brain Injury, 21*(1), 21-29.
- Westerberg, H., & Klingberg, T. (2007). Changes in cortical activity after training of working memory - a single-subject analysis. *Physiol Behav, 92*(1-2), 186-192.
- Willis, S. L., Tennstedt, S. L., Marsiske, M., Ball, K., Elias, J., Koepke, K. M., et al. (2006). Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA, 296*(23).