

Institutionen för Kvinnors och Barns hälsa, Karolinska Institutet

Brain function and behaviour related to development and training of working memory

av

Pernille J Olesen

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Huvudhandledare:

Docent Torkel Klingberg
Karolinska Institutet

Bihandledare:

Professor Hans Forssberg
Karolinska Institutet

Opponent:

Professor Lars Nyberg
Umeå universitet

Betygsnämnd:

Professor Claes von Hofsten
Uppsala universitet
Professor Tom Brismar
Karolinska Institutet
Docent Håkan Fischer
Karolinska Institutet

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ABSTRACT

Training of working memory (WM) is a research field that could result in new therapeutic breakthroughs for people with impaired WM functions. In support of this view, research in our group has previously shown that WM training could increase WM capacity in children with attention deficits and in healthy adults. Apart from that study, there had been no previous literature on WM training presenting clear evidence for a clinically relevant change on WM capacity or brain activity following WM training. Study II and III were designed to investigate these issues.

Only a few previous studies have investigated the development of brain activity related to WM. The results from those previous studies indicate that the development of WM is related to changes in activity in the frontal and parietal cortex. The aim of the developmental studies in this thesis (Study I and IV) was to extend those previous findings using two new approaches: 1) integration of data on brain function and brain structure and 2) investigation of a critical WM function i.e. the ability to ignore distraction.

Previous research in our group showed that increased brain activity in prefrontal and parietal areas underlie the development of WM. In Study I, we sought to investigate how this development is related to the development of brain connectivity. Our aim was to present a network of brain structure and function underlying development of WM, which has previously never been shown. Consistently, the results from Study I showed that development of WM was related to a fronto-parietal network of brain regions where brain activity and connectivity showed a similar developmental trend.

The published research on brain activity related to training of WM is very scarce. Therefore, Study II aimed at investigating the long-term effects of WM training on brain activity using a training paradigm that was designed to optimise the training effects for each individual. For the first time we were able to show that training of a cognitive function, WM, could result in changes in brain activity in the adult human brain in task-related areas.

In Study III the aim was to establish whether WM training could result in clinically relevant effects on performance and behaviour such that it could be used as a new therapy for groups of people with attention deficits. The resulting analyses included data from 44 children, diagnosed with ADHD, who had participated in a five week WM training program. Performance on executive functions, including WM, and behavioural ratings of ADHD symptoms, improved significantly as an effect of WM training.

In Study IV we investigated the development of brain activity related to the ability to ignore distraction. This ability is central to WM since distracting stimuli must be ignored in order to keep information in WM. There is no previous published research on the neural mechanisms underlying the development of this important ability. The unravelling of those mechanisms would add to the understanding of the neurobiology related to disorders affecting attention and impulsivity, in addition to increasing our knowledge about WM functions. Furthermore, Study IV was designed to analyse developmental changes in brain activity related to each phase of a WM task. Importantly, we found that development of WM was related to increased brain activity in frontal and parietal areas during maintenance of information in WM. The ability to ignore distraction was related to brain activity in the prefrontal cortex in adults. In children another part of the prefrontal cortex was related to the presence of distraction and this area corresponded to the area where information was maintained.

To conclude, this thesis demonstrates previously unknown data on the capacity of the human brain in relation to the healthy and deficient WM system and identifies brain areas that are crucial for the development of this system.

SAMMANFATTNING PÅ SVENSKA

När du läser detta dokument försöker du kocentrera dig på innehållet. För att kunna uppfatta och komma ihåg informationen använder du ditt arbetsminne (på engelska "working memory"), dvs du måste hålla informationen uppdaterad i ditt minne under korta perioder för att få ett sammanhang med resten av texten. Du uppnår maximal effektivitet genom att samtidigt ignorera störande moment i omgivningen som tex personer som pratar runtomkring dig. Det vill säga din förmåga att motstå distraktion är avgörande för hur pass bra du kan hålla informationen uppdaterad.

Träning av arbetsminnet är ett forskningsområde som kan resultera i nya terapeutiska genombrott för personer med nedsatt arbetsminneskapacitet. Detta stöds av tidigare forskning i vår grupp som visat att arbetsminnesträning kan öka arbetsminneskapaciteten hos barn med ADHD (en diagnos som karakteriseras av nedsatt koncentrationsförmåga) samt hos friska vuxna. Förutom den forskningen fanns inga tidigare studier, före denna avhandling, på träning av arbetsminnet som visade tydliga bevis för kliniskt relevanta förändringar i arbetsminneskapacitet eller hjärnaktivitet som följd av arbetsminnesträning. Vi studerade effekter av arbetsminnesträning på hjärnaktivitet (Studie II) och beteende (Studie III) hos vuxna respektive barn med ADHD.

Endast ett fåtal tidigare studier har studerat utveckling av hjärnaktivitet relaterat till arbetsminnet. Resultaten från dessa studier visar att utvecklingen av arbetsminnet är kopplat till förändringar av aktivitet i pannloben ("frontal cortex") och hjässloben ("parietal cortex"). Målet med utvecklingsstudierna i den här avhandlingen (Studie I och IV) var att utöka dessa tidigare fynd genom att använda två nya tillvägagångssätt: 1) integrera data på hjärnans funktion (nervcellernas aktivitet) med data på hjärnans struktur (nervbanornas organisation och struktur) och 2) studera en funktion som är kritisk för arbetsminnet dvs förmågan att motstå distraktion.

Inga tidigare studier har visat vilka förändringar i hjärnans aktivitet som ligger bakom utvecklingen av förmågan att motstå distraktion. Ett avslöjande av de mekanismer som ligger till grund för denna förmåga skulle bidra till förståelsen av neurobiologin bakom störningar som påverkar uppmärksamhet och impulsivitet. Samtidigt skulle det öka vår kunskap om arbetsminnets funktioner.

Resultaten från Studie I visade att utveckling av arbetsminnet var kopplat till ett nätverk av områden i pann- och hjässloben där hjärnans aktivitet och struktur visade samma utvecklingsmönster. I Studie IV kunde vi även koppla ökad aktivitet i pann- och hjässloben till förmågan att motstå distraktion. Vi kunde även visa att distraktion störde minnesaktiviteten hos barn medan ytterligare hjärnaktivitet i pannloben hos vuxna ansvarade för att motstå denna effekt.

Resultaten från träningsstudierna (Studie II och III) visade att arbetsminnesträning resulterade i ökad arbetsminneskapacitet hos både barn med ADHD och friska vuxna. Denna ökade kapacitet kunde kopplas till ökad aktivitet i pann- och hjässloben. Baserat på dessa fynd kan vi nu gå vidare och ta fram nya terapimetoder för personer med nedsatt arbetsminneskapacitet. Resultaten har även bidragit till en bredare förståelse för hjärnans förmåga till förändring.

Sammantaget presenterar denna avhandling nya fynd på hjärnans kapacitet i relation till arbetsminnet samt identifierar områden i hjärnan som är centrala för utvecklingen av arbetsminnet.

PUBLICATIONS

This thesis is based on the following studies:

- I** Olesen PJ, Nagy Z, Westerberg H, Klingberg T. Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network. *Cognitive Brain Research* 18: 48-57, 2003.
- II** Olesen PJ, Westerberg H, Klingberg T. Increased prefrontal and parietal activation after training of working memory. *Nature Neuroscience* 7(1): 75-79, 2004.
- III** Klingberg T, Fernell E, Olesen PJ, Johnsson M, Gustafsson P, Dahlström K, Gillberg CG, Forssberg H, Westerberg H. Computerized training of working memory in children with ADHD – a randomized, controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 44 (2): 177-186, 2005.
- IV** Olesen PJ, Macoveanu J, Tegnér J, Klingberg T. Development of brain activity related to working memory and distraction. (*manuscript*)

LIST OF ABBREVIATIONS

ADHD	Attention Deficit/Hyperactivity Disorder
ANOVA	Analysis of Variance
BA	Brodmann Area
BOLD	Blood Oxygenation Level Dependent
D1, D4	Dopamine receptor subtype 1 and 4, respectively
DAT1	Dopamine Transporter gene
DLPFC	Dorsolateral Prefrontal cortex
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4 th edition
DTI	Diffusion Tensor Imaging
EPI	Echo-planar Imaging
FA	Fractional Anisotropy
FEF	Frontal Eye Field
fMRI	Functional Magnetic Resonance Imaging
GLM	General Linear Model
IFG	Inferior Frontal Gyrus
IPS	Intraparietal Sulcus
LTM	Long-Term Memory
MFG	Middle Frontal Gyrus
MNI	Montreal Neurological Institute
MR	Magnetic Resonance
PFC	Prefrontal Cortex
RFT	Random Field Theory
SEM	Standard Error of the Mean
SFG	Superior Frontal Gyrus
SFS	Superior Frontal Sulcus
SPG	Superior Parietal Gyrus
SPL	Superior Parietal Lobe
SPM	Statistical Parametric Mapping
STM	Short-Term Memory
V1	Primary Visual cortex
VLPFC	Ventrolateral Prefrontal Cortex
WM	Working Memory

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1 INTRODUCTION AND BACKGROUND

1.1 How do we learn more about working memory?

One approach to increase the knowledge about a cognitive function is to investigate the neural activity underlying the function and to see how it changes during development. We used this approach in Study I and IV in order to study the development of working memory (WM). Another approach is to interfere with the function and analyse the effect of the intervention on behaviour and/or brain activity. This approach was used in Study II and III in order to investigate the effects of WM training.

1.2 Definition of WM

There are a number of definitions of WM, based on neuropsychological and neurophysiological studies. Central to all definitions is that a key function of WM is to link temporally segregated items of information. The most widely used definition is Baddeley's model of WM (1992), which consists of three components: the visuo-spatial sketchpad, the phonological loop and the central executive. Since Baddeley's model is based on neuropsychological data, which does not include information about brain function, we have chosen another definition of WM.

Our definition of WM is based on neurophysiological studies on primates and has been put forward by Goldman-Rakic and colleagues (1996). According to this definition, WM is the ability to hold an item of information transiently in mind (< 20 s) in the absence of external stimuli. The internal representation of the information guides the behaviour rather than external sensory cues. Further, WM may serve as an *active* workspace where the information can be maintained and manipulated on-line (Engle et al., 1999a). In this sense *active* refers to the constant focus of attention on task-relevant information. Thus, interfering stimuli, both external (e.g. a sensory cue) and internal (e.g. spontaneous thoughts), must be ignored. Consequently, controlled and selective attention are two important parts of WM (Smith and Jonides, 1999). In addition to maintenance of information, WM includes functions that are related to establishing the internal representation that will be maintained, and selecting the appropriate information from this representation.

WM can be categorized according to the type of information that is to be maintained. The type of WM that is studied in this thesis is mainly visuo-spatial WM, which refers to the ability to maintain information about the order and location of items that are presented visually. In Study II and III we have also included measures of verbal WM, which refers to maintenance of phonological information, in order to study transfer effects of WM training.

1.3 WM processes: Domain-specific and domain-general

Classical theories on WM often discuss two different types of WM processes, which interact to create a neural basis for WM (Kane et al., 2004): domain-specific and domain-general processes. Domain-specific processes are involved in the processing of certain types of information, whereas domain-general processes apply to any kind of information. One typical example of a domain-specific process is maintenance of information in WM, which has been shown to involve different brain regions

depending on whether the information is spatial (Courtney et al., 1998) or verbal (Paulesu et al., 1993).

The domain-general processes include those processes that execute, organize and control the domain-specific processes (Smith and Jonides, 1999). These executive processes may interact with domain-specific constructs by controlling and coordinating the maintenance processes while at the same time keeping action plans and goal states active and in easily accessible states. This kind of interaction may facilitate planning and decision-making.

There is a lack of consensus about a classification of executive processes (Smith and Jonides, 1999). The most commonly stated processes include updating of information, inhibition of irrelevant information, shifting of retrieval strategy and dual-task coordination (Baddeley, 1996). Updating refers to the continuous modification of the information in WM according to external (sensory) and internal (long-term memory) cues. These executive functions require a network of brain regions (Collette and Van der Linden M., 2002), including the prefrontal cortex (PFC) and the posterior parietal cortex (Collette and Van der Linden M., 2002; Fuster, 2000; Quintana and Fuster, 1999).

1.4 WM capacity

This thesis includes studies on changes in WM performance and WM capacity as an effect of development and training. Contrary to other memory systems, WM is a limited capacity system (Callicott et al., 1999; Cowan, 2000; Olsson and Poom, 2005). This limitation makes it possible to get a measure of the maximum amount of information that each individual can retain in WM, which is referred to as WM capacity. We study WM capacity since it underlies a wide range of cognitive abilities including reasoning and control of attention (Engle et al., 1999b) and the ability to ignore distraction (de Fockert et al., 2001). Further, this measure is closely related to general intelligence (see section 1.5).

In Study I, II and III we targeted directly the WM capacity for each individual, either by investigating the relation between development of WM capacity and maturation of the brain or by aiming at increasing the WM capacity through WM training. In Study IV, we studied differences in performance reflecting the ability to ignore distraction during development of WM capacity.

No consensus has been reached regarding what the bottleneck of the capacity limitation might be. The various factors that have been suggested include a limitation in the maintenance capacity, processing capacity, rate of decay of information, ability to ignore interference and amount of information attended to at one time. However, much of the research supports a domain-general function underlying the capacity limitation (Engle et al., 1999b; Kane et al., 2004). The evidence for this idea includes factor analyses showing that there is a single factor common to performance on both verbal and visuo-spatial WM tasks (Kane et al., 2004). Additionally, general intelligence correlates with WM capacity as measured from both verbal and spatial WM tasks (see section 1.5).

The results from this thesis may contribute to the disentangling of the source for the WM capacity limitation, although this was not an aim in any study. Study III showed that WM training had effects on non-trained cognitive tasks and on behaviour, supporting the domain-general view of WM capacity. In further support of this view, Study II and IV showed that training and development of WM was related to increased brain activity in the dorsolateral PFC (DLPFC) and posterior parietal cortex, areas that are more involved in domain-general functions than domain-specific (see section 4.2).

1.5 WM capacity and general intelligence

WM capacity is closely related to general intelligence (Conway et al., 2003; Kane et al., 2005; Oberauer et al., 2005) and is the factor that correlates best with measures of general intelligence. Intelligence tests reflect different cognitive abilities but they all have one factor in common, the *g* factor, which is the variance that is shared between all tests. Several studies have shown a strong relation between *g* and WM capacity. (Conway et al., 2003).

Since general intelligence is a broad and poorly defined construct, WM capacity may be a better and more specific measure to understand intelligence. General fluid intelligence, which refers to reasoning ability and problem solving, is more closely related to the *g* factor than crystallized intelligence, which refers to specific knowledge. General fluid intelligence is by definition measured with nonverbal tests. However, the correlation between WM capacity and general fluid intelligence includes tests of verbal WM (Conway et al., 2002), supporting the domain-general view of WM capacity.

It has been suggested that the neural substrate for general fluid intelligence includes recruitment of the WM system since brain activity is found in similar regions during performance of these two functions (Prabhakaran et al., 1997).

1.6 WM and the ability to ignore distraction

The ability to ignore distraction is an important factor that limits WM capacity and affects general intelligence (Dempster, 1991). The WM system is responsible for the control of involuntary shifts in attention, which may occur during distraction. Thus, when WM is highly loaded, the resistance to distracting stimuli is reduced, as compared to when the demand on WM is low (de Fockert et al., 2001). Similarly, people with low WM capacity have a lower ability to ignore distraction than people with high WM capacity (Conway et al., 2001).

Possibly, the ability to ignore distraction depends on executive processes located in the PFC which are responsible for inhibition of sensory processing areas (de Fockert et al., 2001), and stabilization of the internal representation of information in WM (Sakai et al., 2002). The distractor may be processed, instead of ignored, when there is a lack of available WM resources, or when the internal representation is too weak to resist the distractor,

In Study IV, we hypothesized that since adults have higher WM capacity than children they will be less affected by distraction during WM performance and this

would be reflected in differences in brain activity. Accordingly, it was found that brain activity in the PFC could help to explain the differences in the ability to ignore distraction during development.

1.7 Anatomical definitions

- Frontal and parietal cortical areas important to WM

The PFC includes the superior, middle and inferior frontal gyrus (SFG, MFG and IFG, respectively) anterior to the precentral sulcus (Heimer, 1995) (Figure 1).

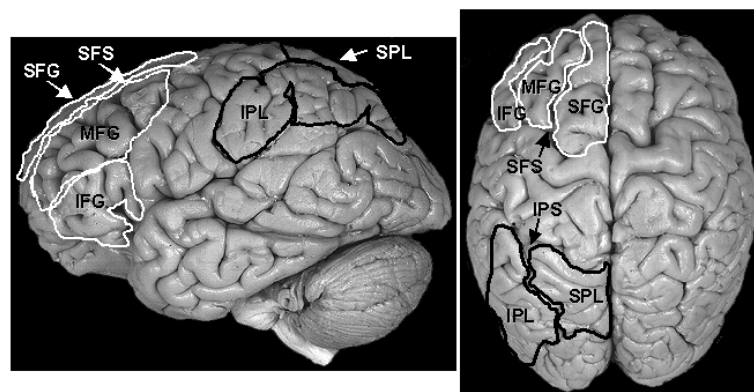


Figure 1 Brain surface anatomy showing the major structures in the prefrontal and parietal cortex. A) Lateral view of the left hemisphere. B) Dorsal view. IFG, inferior frontal gyrus; IPL, intraparietal lobe; IPS, intraparietal sulcus; MFG, middle frontal gyrus; SFS, superior frontal sulcus; SFG, superior frontal gyrus; SPL, superior parietal lobe. Drawings by PJ Olesen, based on Interactive atlases (www9.biostr.washington.edu/da.html).

The DLPFC has been defined in many ways. Most commonly it is defined according to the cytoarchitectonic map created by Brodmann (1909) and includes Brodmann areas (BA) 9, 9/46 and 46 which covers the middle aspect of the superior and middle frontal gyri (Petrides and Pandya, 1999). Based on gyral location the DLPFC has been defined as the part of the frontal lobe that is superior to the inferior frontal gyrus (Fletcher and Henson, 2001). The definition that is used in this thesis includes information about the location of sulci. According to this definition the DLPFC is the middle aspect of the middle frontal gyrus including the inferior and superior frontal sulci (IFS and SFS, respectively), and the gyral surface between them (Luna et al., 2001). This definition was chosen based on the finding that BA 9 covers both the middle and the superior frontal gyri and the architecture of the portion in the superior part is different from the middle part, which is similar to BA 46 (Petrides and Pandya, 1999).

An area specialized for spatial WM has been identified in the caudal part of the PFC. This area is located in the SFS just anterior to the frontal eye field (FEF) (Courtney et al., 1998), which is located in the precentral sulcus (Paus, 1996).

The parietal areas that are mentioned in this thesis include the intraparietal sulcus (IPS) and the inferior and superior parietal lobes (IPL and SPL, respectively) (Figure

1) and are defined according to Duvernoy (1999). The IPS lies on the lateral surface of the parietal lobe, separating the superior and inferior parts. It has an inverted U-shape and extends all the way down to the occipital lobe. The IPL consists of the supramarginal gyrus and angular gyrus. It is located above the lateral fissure with the dorsal margin being the IPS. The SPL includes the superior parietal gyrus and is situated above the intermediate and posterior segment of the IPS.

1.8 The spatial WM network and the flow of information

In order to understand how some of the cortical areas defined above interact to create a neural basis for WM, I will now discuss how visuo-spatial information may flow when it is processed in WM.

WM processes require the coordinated interaction of anatomically distinct brain areas (Constantinidis and Emmanuel, 2004). This interaction is possible due to the direct connections between the prefrontal and the parietal cortex (Schwartz and Goldman-Rakic, 1984) and the high amount of common cortical and subcortical targets of these areas (Selemon and Goldman-Rakic, 1988).

The processing of visuo-spatial information in WM starts in the primary visual cortex (V1) and continues along the dorsal visual stream (Ungerleider et al., 1998), which runs from V1 to the posterior parietal cortex. Stimulus processing may be completed in the posterior parietal cortex and the activity transferred without further modification to the SFS (area 8 in (Chafee and Goldman-Rakic, 1998)). The information may then be transferred to the DLPFC, which is interconnected with the SFS (Petrides, 2000).

Feedback projections from the PFC may control functions located in posterior association cortex (Tomita et al., 1999) in order to select task-relevant neural mechanisms (Van der Velde and de Kamps, 2001). This top-down control (i.e. the flow of information from “higher” to “lower” brain areas (Corbetta and Shulman, 2002) in the processing hierarchy) may alter the transfer of information from visual cortex to the parietal cortex such that more processing is devoted to task-relevant information (Fuster et al., 1985; Tomita et al., 1999; Van der Velde and de Kamps, 2001). Furthermore, top-down processes may be involved in creating a more stable representation of the information in WM. One way to achieve this could be by means of the DLPFC increasing the correlation of activity between the SFS and the parietal cortex (Sakai et al., 2002), through the direct connections between the SFS, DLPFC and parietal cortex (Petrides and Pandya, 1984).

The idea that there is no hierarchical distinction in the processing between the SFS and the parietal cortex was first expressed by Chafee and Goldman-Rakic (1998). Factors that support this idea include: simultaneous recruitment of the PFC and the parietal cortex during performance of a WM task (Chafee and Goldman-Rakic, 1998), cooling of either the prefrontal or the parietal cortex has similar effects on the shared activity (Chafee and Goldman-Rakic, 2000) and lack of data showing that the connections between the PFC and the parietal cortex are of the feedforward and feedback type.

A crucial aspect in the flow of WM-related information in the brain is the link between sensory activity and memory activity. This link may be established as early as in V1 (Super et al., 2001). In a study by Super et al. (2001) activity in V1 was recorded while monkeys were performing a delayed-response task. It was found that contextual modulation, i.e. enhancement of the sensory response, was related to an active maintenance of task-relevant information, rather than a passive, less goal-oriented, process. It is possible that this link is strengthened by direct feedback projections from the PFC to early visual processing areas (Barbas, 1988; Makris et al., 2005; Pandya and Yeterian, 1990).

1.9 Models of PFC function in WM

The functional organization of the PFC, in relation to WM processes, is largely debated. One model segregates the areas of the PFC according to the type of process (the process-specific model). In this model, maintenance functions are thought to reside in the ventrolateral PFC (VLPFC) whereas the dorsolateral part is recruited only when manipulation of information is required (Owen, 1997; Petrides, 1995). Another model segregates the PFC according to the specific type of information that is processed (the domain-specific model). This model suggests that spatial information is maintained in the DLPFC and object information in the VLPFC (Ungerleider et al., 1998; Wilson et al., 1993). However, more recent studies have led to modifications of this model by showing that it may be the SFS, rather than the DLPFC, that is responsible for maintenance of spatial information (Courtney et al., 1998) (see section 4.2).

The results from this thesis suggest that the functions of the frontal and parietal areas involved in visuo-spatial WM may be organized according to the demand of the task. The SFS and posterior association areas may be sufficient to maintain spatial associations on low demand trials. Higher demands, such as an increase in load (Rypma et al., 1999) or when the task includes manipulation (Glahn et al., 2002) or monitoring (Petrides et al., 1993) of information, may require additional recruitment of the DLPFC. The specialization of WM functions in frontal and parietal areas will be discussed more extensively in the general discussion.

1.10 Dopamine and WM

There are a number of crucial findings pointing towards the importance of the dopamine system for the modulation of WM functions (Ellis and Nathan, 2001). First, alterations in the dopamine system, such as in Attention-Deficit/Hyperactivity Disorder (ADHD) (Faraone et al., 2001), Parkinson's disease (Lewis et al., 2005) and Schizophrenia (Goldman-Rakic et al., 2004), are related to impaired WM functions. Second, dopamine may have a facilitating effect on visuo-spatial WM. Administration of methylphenidate, a drug that increases the amount of dopamine in the synapse (see section 1.12), to healthy adults was found to improve performance on a spatial WM task (Elliott et al., 1997). Studies in monkeys suggest that dopamine has a facilitating effect on visuo-spatial WM through the binding onto D1-receptors (Sawaguchi, 1991; Sawaguchi, 2001). These data are consistent with models of WM, which suggest that dopamine increases the signal-to-noise ratio of the activity representing the memorized information (Brunel and Wang, 2001; Cohen et al., 2002). Third, the PFC,

a key node in the WM network, receive the most prominent dopaminergic innervation of all cortical areas (Brown et al., 1979; De Keyser et al., 1989; Lindvall et al., 1974).

However, the effects of dopamine on WM are complex. Different subtypes of the dopamine receptor mediate distinct effects, which are related to the phases of a WM task (Wang et al., 2004) and in the human brain the dopaminergic innervation of posterior areas may be as high as that in frontal areas (De Keyser et al., 1989).

1.11 Development of WM

- Quantifying WM capacity, changes in capacity over time and how those changes are related to brain development

Methods that measure the changes in WM during development usually use a span procedure, in which the amount of information to be maintained in WM changes according to the child's performance. Changing the number of items in a sequence sets the demand on WM. If the child recalls all items correctly the sequence is extended with one item. In most cases the child must successfully recall two unique sequences on the same level before reaching the next, higher level. The task ends when the child fails to recall two sequences on the same level. The memory span is defined as the maximum amount of information that the child can recall successfully and is the most commonly used measure of WM capacity. This approach was used in the present thesis in order to study changes in WM capacity. Another possibility would be to vary the delay period and follow developmental changes in the extent of time a child can retain the memorized information (Diamond and Doar, 1989).

WM capacity increases (Fry and Hale, 2000; Gathercole, 1999; Luna et al., 2004; Westerberg et al., 2004) and the ability to ignore interference improves (Dempster, 1992; Hale et al., 1997; Ridderinkhof et al., 1997; Tipper et al., 1989) during childhood development. The most extensive change in the development of WM capacity is seen before adolescence when WM capacity may expand 2-3 times (Gathercole, 1999). In fact, the development of WM starts already during the first year of life. Infants, who were 6 months old at the start of the experiment, could perform a delayed response task with increasingly longer delay intervals as their brains matured during the following 6 months (Diamond and Doar, 1989).

The functions that may underlie the increased WM capacity during development include increased controlled attention and processing efficiency and improved use of strategies such as chunking and rehearsal (Fry and Hale, 2000; Gathercole, 1999). These functions may also be responsible for the increased capacity during WM training (see section 4.4).

In this thesis we have investigated development of visuo-spatial WM, including both retention of static visual patterns and retention of sequences of items. It has been suggested that the memory for static patterns develops faster than the memory for sequences of items (Logie and Pearson, 1997; Pickering, 2001). This may be related to the more complex functions included in the retention of sequences of items as compared to the memory for a static visual pattern. Generally, more complex cognitive functions develop later than simpler functions, such as primary sensory functions (Fuster, 2002). This is paralleled by a lag in the development of the PFC,

which is responsible for higher cognitive functions, compared to other cortical regions (Fuster, 1989; Giedd et al., 1999; Huttenlocher and Dabholkar, 1997; Sowell et al., 1999). The DLPFC is one of the last brain regions to mature and gray matter density in this region does not reach adults levels until the second decade of life (Giedd, 2004). This region is important for the control of impulses and for the ability to ignore distracting stimuli. The development of brain activity underlying this ability was investigated in Study IV.

The neural bases for the shaping of the brain during development include synaptic sprouting (i.e. formation of new synapses) and synaptic pruning (i.e. retraction of existing synapses) as well as white matter maturation. During the first decade of life there is a substantial overproduction of synapses. Synaptic density peaks around five years of age and adult levels are reached in mid-adolescence (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997). The changes during adolescence in gray matter density occur in parallel with an increase in white matter volume, i.e. more connections are established between the neurons (Giedd, 2004; Paus, 2005; Sowell et al., 1999; Sowell et al., 2004). White matter density and volume increases steadily during childhood and adolescence (Giedd et al., 1999; Schmithorst et al., 2002) whereas gray matter volumes show an inverted U-shape, peaking around mid-adolescence (Giedd et al., 1999; Giedd, 2004). This has lead researchers to suggest that the improved cognitive functions in adolescence are related to improved communication between brain regions (Sowell et al., 1999).

Studies on the development of brain function show that children activate similar areas as adults during performance of spatial WM tasks (Casey et al., 1995; Nelson et al., 2000; Thomas et al., 1999). Direct comparisons between children and adults show that the increase in WM capacity during childhood occurs in parallel with an increase in activity in fronto-parietal areas (Klingberg et al., 2002a; Kwon et al., 2002; Luna et al., 2001) and maturation of white matter in the prefrontal lobes (Klingberg et al., 1999; Nagy et al., 2004). Thus, these data indicate that improved communication between frontal and parietal brain regions may underlie the development of visuo-spatial WM. We investigated such a relationship in Study I by combining measures of brain activity with measures of brain connectivity in areas related to the development of WM.

1.12 ADHD

- A developmental disorder that targets the WM system - Symptoms, neurobiology and treatment

ADHD affects about 3-5% of school-age children and is one of the most prevalent conditions in child psychiatry (Castellanos and Tannock, 2002; Socialstyrelsen, 2002). The diagnosis is based upon criteria stated in DSM-IV (American Psychiatric Association, 1994), which include symptoms related to inattention, hyperactivity and impulsivity. Children with ADHD often experience poor school achievement, problems with social interactions and low self-esteem (Socialstyrelsen, 2002). These problems can be related to a core deficit in executive functions, specifically deficits in WM, response inhibition, temporal processing and delay aversion (Castellanos and Tannock, 2002). There is substantial evidence showing that spatial WM is impaired in children with ADHD (Barnett et al., 2001; Dowson et al., 2004; Karatekin and

Asarnow, 1998; Westerberg et al., 2004) and spatial abilities may be more impaired than verbal (Martinussen et al., 2005).

The aetiology is unclear but specific genetic variations have been associated with ADHD. A particular variation in the dopamine transporter gene, DAT1, and a variant in the dopamine receptor gene, D4, are more common in children with ADHD (Cook, Jr. et al., 1995; Faraone et al., 2001). Further, ADHD is related to alterations in brain function and brain size. During performance of spatial WM tasks, children with ADHD have reduced activity in the PFC and the basal ganglia compared to normally developing children (Giedd et al., 2001). The growth curves for brain volumes in children with ADHD and normally developing children are parallel (Castellanos et al., 2002) but the curves for children with ADHD are significantly below that for normally developing children. Thus, the abnormal influence on brain development in ADHD occurs early in life and persists throughout development. The caudate nucleus is the only brain structure that does not follow this developmental pattern. During late adolescence the volume of the caudate is not significantly different from normally developing children (Castellanos et al., 2002), which may be related to the decrease in hyperactivity and impulsivity symptoms during this age period.

The most common treatment for ADHD is medication with stimulant drugs such as methylphenidate (Ritalina®). Methylphenidate blocks the dopamine and norepinephrine reuptake thereby increasing the amount of neurotransmitters in the synaptic cleft (Robbins, 2002). As mentioned earlier (section 1.10), it has been shown that methylphenidate can increase WM performance in healthy adults (Elliott et al., 1997). However, the reason for the therapeutic effects on ADHD symptoms is unclear.

Other treatments include psychosocial treatment such as cognitive behavioural therapy and educational interventions (Barkley, 2002). These treatments improve the prognosis for children with ADHD, but it requires long-term, regular treatment. A large-scale study, comparing treatments for ADHD, showed that medication was more effective than psychosocial treatment, and could not find any additional effect of psychosocial treatment on ADHD symptoms when it was used in combination with medication (MTA Cooperative Group, 1999). However, the combined treatment provided advantages for non-ADHD symptoms. Despite this effectiveness of pharmacological treatment, parents and teachers prefer non-medication therapies (Bukstein, 2004).

No previous study has specifically targeted WM in the treatment of ADHD. In Study III we hypothesized that WM training would improve WM in children with ADHD and that the training effect would generalize to other cognitive functions and improve the symptoms of ADHD. The results were highly significant in favour of this hypothesis suggesting that WM training could be used in the treatment of ADHD symptoms either alone or in combination with other treatments.

1.13 Skill learning

- Apart from development, is it possible to increase the WM capacity? - Brain reorganization in the adult brain

The WM training that was applied in Study II and IV can be categorized as cognitive skill learning according to the division of memory systems presented by Squire and Zola-Morgan (1988). Skill learning refers to learning a new behavioural capacity gradually over time, without any explicit, declarative knowledge (Poldrack et al., 1999). The WM training in Study II and IV was implicit, non-declarative, and learning occurred gradually over time. The training was procedural since the subjects engaged in the procedure in which the knowledge was embedded in order to learn the skill.

The study of changes in brain reorganization as an effect of training and learning is an important research area, since it investigates the latent potential of the brain, which may be the target for many therapies. There is evidence that cortical activation patterns exhibit flexibility related to learning (Sanes and Donoghue, 2000) and neuroimaging has contributed substantially to this field of research.

Only a few previous studies have investigated the effect of long-term skill learning on changes in brain reorganization in the healthy human brain. In a review of published studies, searchable in PubMed, a total of 27 such studies were found. Of these, 12 studies investigated motor skill learning, 11 studies looked at perceptual learning and 4 studies reported data on cognitive skill learning (including Study IV). It should be emphasised that this review did not cover all the publications in this field.

Specifically, the motor skill learning literature is extensive and some publications may have been forgotten. However, based on the search criteria for this review (see section 4.9), the majority of the publications should have been targeted. All the studies in the review on cognitive skill learning (Hempel et al., 2004; Little et al., 2004; Olesen et al., 2004; Qin et al., 2003) were published within the last two years, showing the news value of this field of research. The previous studies on skill learning do not give a clear answer to how training may affect brain reorganization. The spectrum of findings include training-related increased (Hempel et al., 2004) and decreased (Schultz et al., 1999) activity in task-related areas or both increased and decreased activity (Poldrack and Gabrieli, 2001), extension (Karni et al., 1995) or reduction (Little et al., 2004) of an area that was activated before training and recruitment of new areas (Wang et al., 2003). The review will be discussed further in section 4.9.

We hypothesized that in parallel with increased WM capacity, WM training would lead to increased brain activity in task-related areas, i.e. areas that were already involved in performance before training. An alternative hypothesis could be that new areas would be recruited after training implying a shift in cognitive strategy for task resolution.

1.14 WM on the cellular level

- Internal representation of information

Critically, WM is characterized by the ability to sustain the pattern of activity that is present during perception, after removal of the stimulus. To date, the best candidate for a neural correlate of this function is persistent delay-period activity (Funahashi et al., 1989; Fuster and Alexander, 1971). When information is maintained in WM, neurons in certain brain regions fire consistently without the need for sensory input, thereby forming the basis for an internal representation of the information.

Persistent delay-period activity in prefrontal neurons was first shown by Fuster and Alexander (1971). This finding has been supported by later work (Funahashi et al., 1989; Funahashi et al., 1993) and delay-period activity has been found in several other cortical and subcortical areas including the inferotemporal cortex (Fuster et al., 1985), the posterior parietal cortex (Chafee and Goldman-Rakic, 1998), the cingulate cortex (Niki and Watanabe, 1976), the basal ganglia (Hikosaka and Wurtz, 1983) and the mediodorsal thalamic nucleus (Fuster and Alexander, 1973). Consequently, persistent delay-period activity is now considered as a central neural mechanism for WM and is included in models of WM (Camperi and Wang, 1998; Constantinidis and Wang, 2004; Durstewitz et al., 2000b; Tegner et al., 2002). Many of the areas where delay-period activity is found have reciprocal connections with the PFC (Fuster, 1989; Goldman-Rakic, 1988).

A unique characteristic for the sustained activity in the PFC is the resistance to distracting stimuli presented during the delay (Miller et al., 1996). In contrast, sustained activity in the inferotemporal cortex vanishes gradually when a distracter is presented (Miller et al., 1996). Further evidence for the mnemonic function of prefrontal neurons is that these neurons have specific memory fields. Certain neurons code the same location over and over again and the coded location varies between neurons (Funahashi et al., 1989). Also, the delay-period activity changes according to the duration of the delay, suggesting that the activity is dynamic and specifically coupled to the memory of the cued information (Funahashi et al., 1989).

1.15 Neural mechanisms for persistent delay-period activity

Ever since it was first shown by Fuster and Alexander (1971) that persistent delay-period activity underlies WM, it has been a central target for researchers to understand how cortical neurons can sustain discharges without sensory input. Today, we have come closer to the unravelling of this mystery, and the clues derive from neurophysiological studies (Goldman-Rakic, 1995) and computational simulations of neural networks (Compte et al., 2000; Tegner et al., 2002; Wang, 2001).

In analogy with the columnar organization of the primary visual cortex, Goldman-Rakic (1995) and colleagues (Kritzer and Goldman-Rakic, 1995) suggested that the neural basis for persistent activity is organized within functional columns in the PFC. This view, suggesting that the PFC may itself be able to sustain the persistent activity by means of local recurrent excitatory connections (Gonzalez-Burgos et al., 2000; Kritzer and Goldman-Rakic, 1995) is still the most well-established theory on the neural basis for persistent activity (Wang, 2001). Today, both excitatory and

inhibitory neurons are thought to be involved in the local recurrent activity (Constantinidis et al., 2002; Tegner et al., 2002; Wang, 2001).

Extending this theory to a more detailed neuronal level, the recurrent synapses may be boosted by synaptic augmentation (Hempel et al., 2000), referring to temporal strengthening of synapses. Synaptic augmentation is present in the PFC but absent in visual cortex (Hempel et al., 2000), supporting the idea that temporal synaptic strengthening may be important for specific prefrontal functions such as synaptic reverberation.

Contemporary models of recurrent activity have shown that when dopamine is added to the network, the signal-to-noise ratio is increased (Durstewitz et al., 2000a). Since the PFC is heavily innervated by dopaminergic projections (Brown et al., 1979; De Keyser et al., 1989; Lindvall et al., 1974), it was suggested that the dopamine-related increase in recurrent activity may be involved in creating a distractor-resistant representation of information in WM (Constantinidis and Emmanuel, 2004).

Finally, the persistent activity is thought to be a network function since it can last for several seconds, which is much longer than the time constants of single-neuron biophysical processes (Constantinidis and Wang, 2004). However, graded persistent activity has been found also at the single neuron level (Egorov et al., 2002) which suggest a more complex mechanism underlying persistent activity.

1.16 WM in relation to other cognitive functions

1.16.1 *Attention*

One commonly used description of the relationship between spatial WM and spatial attention is related to rehearsal of spatial information. In order to maintain spatial information it may be necessary to rehearse the spatial locations, which is achieved by repeatedly shifting attention towards each location (Awh and Jonides, 2001). Accordingly, impaired performance due to interference has been explained as a shift in attention away from the relevant information, which interrupts spatial rehearsal (Smyth, 1996).

There is no doubt that attention is important to, and interacts with, WM. The working theory in this thesis is that attention is a crucial part of WM, which has also been suggested in previous theories where attention is included as an executive process (Smith and Jonides, 1999). Further supporting this view is the functional overlap of brain regions activated during spatial attention and spatial WM (Awh and Jonides, 2001; LaBar et al., 1999). Specifically, the interactive fronto-parietal network may be the link between spatial attention and spatial WM, a suggestion that has been expressed by Awh and Jonides (2001): "the frontal and parietal mechanisms involved in spatial working memory are an attention circuit that operates in the service of memory".

1.16.2 *Short-term memory*

The modern models of WM are different from the early definition of short-term memory (STM) as a unitary system (Richardson, 1996). Today, WM is commonly distinguished from STM in that it is a more active form of memory that requires controlled attention (Engle et al., 1999a). According to this distinction, WM can be thought of as reflecting the ability to maintain the activation of memorized items in the focus of attention. On a neural level, the focus refers to activity above a certain threshold. Further, the more effortful processing that is needed the more WM, relative to STM, is engaged (Conway et al., 2002). Therefore, a certain task cannot simply be referred to as a STM or a WM task since people with different WM capacities may require different amounts of processing. For instance, children may perceive a certain task as effortful whereas adults perform the same task easily. The task would then be considered a WM task for children but a STM task for adults. In addition, no task is a pure measure of either STM or WM capacity. Tasks that measure one construct probably include the other construct to some extent.

Taken together, the concept of a multi-component WM has more or less replaced the idea of a unitary STM by including STM in the concept of WM (Engle et al., 1999a). The working theory in this thesis is that WM is a combination of specific functions including temporary maintenance of information and general functions related to executive processes and that active maintenance requires WM. Active maintenance refers to maintenance during distraction, rehearsal and/or manipulation of information. Based on this working theory we refer to the tasks used in this thesis as WM tasks. It is important to emphasize that the categorization of a certain task as a WM or STM task may be extra difficult in the visuo-spatial domain, in which STM and WM are more closely related than in the verbal domain (Miyake et al., 2001).

1.16.3 *Long-term memory*

I will only briefly comment upon the distinctions between WM and long-term memory (LTM) since this is not an issue that has been discussed in relation to any of the studies, but it may be of interest for certain readers. First, the functional characteristics of LTM and WM suggest two separate systems. LTM is dedicated to storing memories over long periods of time, requiring that they do not vanish immediately. This is achieved by structural changes at the level of the synapse (Abraham and Williams, 2003). WM is dedicated to processing of information during short periods of time and the information may vanish when it is not relevant any more. This kind of information processing is achieved by recurrent activity within neuronal populations (see section 1.15). Second, different areas in the brain are crucial for each type of memory. The hippocampus is crucial for storing representations in LTM as evidenced by impaired LTM in patients with amnesia, causing damage to this region (Squire and Zola, 1998). WM requires the prefrontal and parietal cortex (Chafee and Goldman-Rakic, 2000). However, both WM and LTM require networks of areas in order to function properly and some of the brain areas are shared between the WM and LTM network (Cabeza et al., 2002; Naghavi and Nyberg, 2005).

2 METHODS

2.1 Neuropsychological tests

The neuropsychological tests that were used in Study II and III for the evaluation of training effects included tests on executive functions and problem solving. The Corsi block task and the Span board task measure visuo-spatial WM, the Stroop task measures response inhibition, the Digit span task is a test on verbal WM and Raven's progressive matrices is a test on problem solving. In all analyses the effects were compared to a control group that did not participate in training (Study II) or that underwent low dose training (Study III).

2.2 WM tasks

The WM tasks that were used during scanning and included in the training program were based on a common basic structure, including cue presentation, delay and response. In all the tasks used during scanning the cue consisted of circles. For these tasks the participant had to either maintain information about the location of the cue on the computer screen (Study I and IV) or both the location and the position of the cue in the sequence (Study II). Thus, all the tasks used during scanning were visuo-spatial WM tasks. Some of the tasks used in the training program were verbal WM tasks i.e. a sequence of verbal cues should be memorized and recalled. The WM training program in Study II, Experiment 1, included one visuo-spatial and two verbal WM tasks. In Study II, Experiment 2 it included three different visuo-spatial WM tasks and in Study III the training program consisted of multiple visuo-spatial and verbal WM tasks.

2.3 Functional Magnetic Resonance Imaging

2.3.1 General overview

Brain activity was measured with functional magnetic resonance imaging (fMRI). In fMRI there is no need for radioactive tracers since the technique is based on deoxyhemoglobin as an endogenous paramagnetic contrast agent. A reduction in the concentration of deoxyhemoglobin results in an increase in the T2*-weighted MR signal. The concentration of deoxyhemoglobin can change either by decreasing the amount of deoxygenated blood or by increasing the amount of oxygenated blood. Thus, it is the relative amount of deoxygenated to oxygenated haemoglobin that determines the signal. This effect is known as the blood oxygenation level dependent (BOLD) effect. It has been shown that the oxygenation of the venous blood in the human brain is elevated when neurons are activated (Fox and Raichle, 1986). This effect seems to be related to an increase in cerebral blood flow rather than a local change in oxygen consumption (Fox et al., 1988; Fox and Raichle, 1986). Based on these findings, the BOLD contrast was found to be a successful way to measure human mental functions (Ogawa et al., 1992).

The fMRI data in this thesis were preprocessed to render them smooth and normalized before they were analysed. The analysis was performed using SPM99 (Study I and II) and SPM2 (Study IV) according to the following scheme:

1. Set up the model. Choose the factors that best explain the appearance of the data.
2. Estimate the parameters for each voxel.

3. Calculate the significance of the effect in each voxel according to the chosen alpha value (i.e. the number of false positives).

The analyses of functional activations were based on the general linear model (GLM). The GLM's for each study contained a set of basis functions, modelling the specific paradigm, and estimates of confounding effects such as motion estimates. The degree to which the basis functions modelled a significant amount of variance in the time course of the BOLD signal was estimated in the GLM. To get a better fit of the parameter estimates, the basis functions were convolved with the canonical haemodynamic response function. The random field theory (RFT) was applied to the data to control for false positives. The RFT is a branch of mathematics that deals with smooth, spatially extended data and applies well to fMRI data. The time courses of adjacent voxels tend to be correlated due to smoothing of the data and low resolution.

Random-effects group analyses were performed using the subject-specific summary statistics approach implemented in SPM (Penny and Holmes, 2004). Inferences were made at the cluster-level based on *t*-statistics. The data in Study I and II were correlated with WM capacity in simple regression models. In Study IV group interactions were analysed using two-sample *t*-tests. In all studies the main effect was calculated using one-sample *t*-tests. Significant cluster *p*-values were corrected for multiple comparisons using the RFT. Brain activity related to a certain function was expressed as per cent signal change relative to a global mean intensity of 100.

2.3.2 The logic of subtraction

Experimental conditions were compared, by applying the subtraction method, in order to observe a change related to WM functions. A central assumption in this method is that it is possible to isolate neural mechanisms related to a specific cognitive function. The basic steps in the subtractions that were applied in this thesis include:

1. A control task was constructed for each WM task that was studied. The control task was similar to the cognitive task in perceptual and motor aspects but did not include any requirement for memorization.
2. fMRI data of brain activity related to each of the two tasks was collected.
3. The difference in brain activity between the two tasks was analysed at the individual level. The assumption was that brain areas that are uniquely involved in the WM task mediate WM processes. Thus, brain activity related to other functions (perceptual and motor functions) was subtracted away, leaving activity specific to WM functions.

2.4 Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) was used in Study I to get indirect information about brain structure by measuring the diffusion of water molecules. The MR signal was sensitised to diffusion by inserting diffusion gradients into a spin-echo EPI sequence. The diffusion tensor represents the displacement of water molecules in the tissue and the probability of finding a molecule at a certain position at any given time. In the brain, the diffusion is relatively more isotropic (i.e. spherical diffusion ellipsoid) in cerebrospinal fluid and grey matter and more anisotropic (i.e. elongated diffusion ellipsoid) in white matter. Fractional anisotropy (FA) was used as a measure of how much the diffusion ellipsoid deviated from a sphere. FA is a scalar measure of the 6-

dimensional information in the diffusion tensor. Thus, it includes information about the shape, size and skewness of the diffusion ellipsoid. In this thesis FA values above 0.15 were defined as representing voxels that were occupied mainly by white matter.

3 THE STUDIES: RESULTS AND COMMENTS

3.1 Study I

The relationship between the development of human brain function and structure underlying WM is not well known. We hypothesized that by investigating the relationship between brain activity, white matter maturation and WM capacity, it would be possible to identify a network of brain regions related to the development of WM. Our approach was to collect WM capacity scores from 23 children aged 8-18 years and to correlate these values with measures of white matter maturation and brain activity, respectively.

White matter maturation was evaluated with values of FA using DTI and BOLD response values were used as indicators of brain activity in analyses of fMRI data. Peak voxel values were extracted from the areas where correlations were found. The values extracted from the FA-WM correlation were then used as covariates in the fMRI analysis of WM. To confirm these findings, a similar correlation was performed by including the values extracted from the BOLD-WM correlation in the DTI analysis. The hypothesis was that brain areas where activity was found to be important for the development of WM would correlate with values of white matter maturation lying in the vicinity of those areas.

WM capacity was measured outside the scanner and was calculated as the total number of correctly recalled circles on all levels. There was a significant correlation between WM capacity and age (Pearson's $r = 0.50$, $n = 23$, one-tailed $p < 0.01$) (Figure 2). Performance during scanning showed ceiling effects and there was no effect of age on performance.

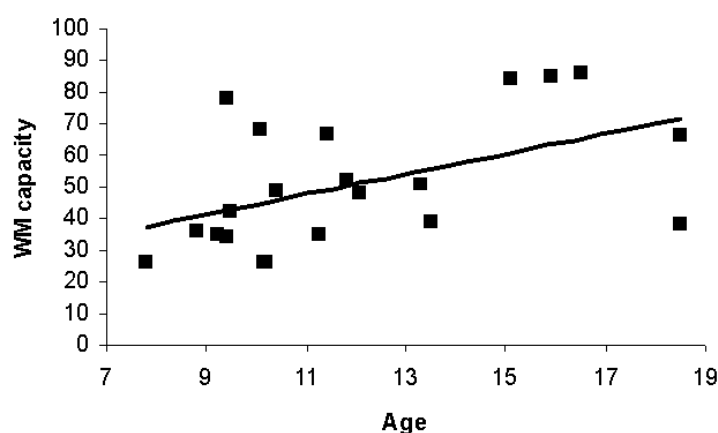


Figure 2 WM capacity increases during development (Study I).

Brain activity (BOLD) related to the development of WM capacity was found in the frontal and parietal cortex and in the caudate nucleus. Studies on non-human primates have shown that there are strong connections between homologous frontal and parietal areas in the monkey brain (Petrides and Pandya, 1984; Selemon and Goldman-Rakic, 1988). Consistently, FA values of the superior fronto-parietal white matter correlated with BOLD response in the SFS and intraparietal cortex. We were able to explain the correlations based on the information about fibre tracts derived from tracing studies in non-human primates. Unfortunately, the literature on DTI tracings is too scarce to show similar patterns of connectivity in the human brain and these data are coarser than those from invasive tracing in animals. However, consistency between animal and human connectivity patterns has been shown using DTI (Parker et al., 2002). Developmental changes in white matter may include increased myelination and organization of axons and increased axonal diameter (Basser and Pierpaoli, 1996).

The way we chose to analyze the data may give the impression that the correlations between FA values and BOLD response would be evident. The values that were selected were chosen based on the correlation with WM and WM had already been found to correlate with certain areas. However, not all extracted values correlated with all areas that had been found to correlate with WM. This suggests that there must be something unique that contributes to the correlation. I will try to explain what might be going on. The extracted values were chosen based on their correlation with WM capacity scores. Thus, the variance shared by these vectors reflects the developmental aspect of the values. Furthermore, for each vector there was a portion of unique variance, since no vector showed 100% correlation with WM capacity. The unique variance contributed to determine which brain area each vector would correlate with. Consistently, there was relatively stronger correlation between certain grey and white matter areas, and these variations in correlation pattern gave rise to a network of areas related to the development of WM.

In addition, I suggest that the results derived from the correlation between extracted FA values and BOLD response (Study I, Table 3, upper part) are more reliable than those derived from the correlation between extracted BOLD response and FA values (Study I, Table 3, lower part). FA values represent a measure that may be relatively stable. It reflects the diffusion of water molecules in the brain, which is a non-static measure, but the diffusion is affected only by parameters that are static (at least in the short-term) such as myelination, axonal diameter and fiber tract organization. The BOLD response values are probably less consistent measures. The BOLD effect is a vascular response, which arises from event-related changes in blood flow and blood oxygenation. Thus, subtle variations in BOLD response, contributing to the unique variance in the BOLD vectors, may give a less reliable measure of variations in brain activity than small variations in FA.

3.2 Study II

It was previously largely unknown if the neural mechanisms underlying WM capacity were able to reorganize in the adult human brain. We investigated this phenomenon by administering a 5-week WM training program to 11 healthy adults and evaluating the training effects on brain activity using fMRI. Scanning took place before and after the training, and also during the training in 8 subjects. The effects of training were also evaluated by the administration of neuropsychological tests before and after the training.

It had previously been shown by our group that the increase in WM capacity that is related to development is based on increased activity in the frontal and parietal cortex (Klingberg et al., 2002a; Olesen et al., 2003). We hypothesized that an increase in WM capacity related to training would have the same neural basis and would correlate with the gradual increase in WM capacity. Therefore, training-related changes in brain activity were identified by correlating brain activity in the whole brain with scores representing the WM capacity that each subject had reached during each scan. These scores correlated with the level of WM capacity that the subjects had reached in the training program outside the scanner (Pearson's $r = 0.88$; one-tailed $p < 0.05$).

The results were in agreement with our hypothesis and showed that brain activity in frontal and parietal areas increased after training, in parallel with improved WM capacity. The neuropsychological test data indicated effects of generalization. There was no change in strategy use as reported from the participants. Most of the subjects reported that they used chunking as a strategy throughout the training.

In support of these results, Vogel et al. (2004) have recently shown a relationship between visual WM capacity and neural activity such that high capacity was related to high activity. The increased activity in parietal and frontal areas may reflect increased maintenance capacity (Todd and Marois, 2004) and increased top-down control (Curtis and D'Esposito, 2003), respectively. The top-down control may work by repetitively focusing attention on the maintained information (Curtis and D'Esposito, 2003; Todd and Marois, 2004), thereby creating a more robust representation.

A crucial aspect for the clinical relevance of WM training is the long-term effect of the training. To investigate this, the subjects were scanned and tested again three months after the training had stopped (scan 6; unpublished data). Performance on both low load (level 5) and high load (level 7) trials was significantly higher on scan 6 compared to scan 1 (Figure 3a). On low load trials, performance (i.e. the number of correctly recalled circles) continued to increase from scan 5 to scan 6, whereas it dropped on high load trials (Figure 3a). Reaction times did not change from scan 5 to scan 6. Thus, even without any training, performance had improved compared to before training suggesting that the effect of training generalized to activities in the daily life creating a positive feedback loop, which was efficient at least during three months.

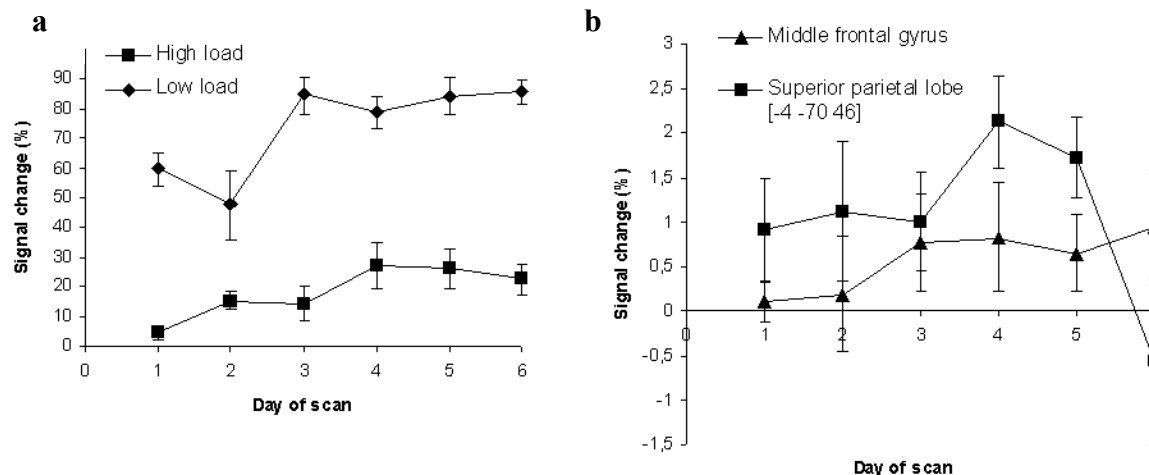


Figure 3 The effect of WM training on a) performance and b) signal change. a) Performance, during training (scan 1-5) and 3 months after the five-week training period (scan 6), for high and low load WM trials. b) Signal change in the middle frontal gyrus and superior parietal lobe during and after WM training. Standard error of mean (SEM) is included.

Brain activity increased in the frontal lobe but decreased substantially in the parietal lobe three months after training had stopped (Figure 3b). It may be that the function of the frontal area is more general than that in the parietal cortex (see section 4.2). A more general function may be involved in several daily activities and will therefore get continuous input even without specific training. Such general functions include keeping goal states and action plans in mind and updating of the relevant information (see section 1.3). However, an area that is more specialized in a certain function may not as easily be stimulated since there is no constant need for this area.

There is to my knowledge, only one additional study that has investigated the effects of long-term WM training on brain activity in healthy adults (Hempel et al., 2004). In that study, the n-back task was trained for four weeks at three prefixed levels of complexity. In support of our findings, that study showed increased activity in the MFG and intra/superior parietal lobe as performance increased over time. However, they reported that activity dropped to pre-training levels when performance reached asymptote. In our study, we did also see a decrease in activity at scan 5 (Figure 3a), but the level of activity was still higher than before training. The main difference between our study and Hempel et al. (2004) is that we applied an adaptive training paradigm that changed according to each subject's current level of performance. This paradigm was applied in order to reach the training level that most efficiently would increase the capacity for each subject. It may be that this training paradigm resulted in more stable training effects, lasting for longer periods of time.

3.3 Study III

Impaired WM is a central factor underlying the symptoms included in ADHD (see section 1.12) (Castellanos and Tannock, 2002). Based on a previous study from our group (Klingberg et al., 2002b) we hypothesized that WM training would improve WM capacity in children with ADHD. Further, since the WM functions recruit higher order association areas in the brain, we speculated that the effect of training would

generalize to non-trained tasks. Additionally, we expected that this would be related to a reduction in ADHD symptoms.

Fifty-three children diagnosed with ADHD were recruited from four clinical sites. The children were randomly assigned to either a training group or a comparison group. All children undertook computerized WM training for five weeks. For the children in the training group the level of the tasks was adapted to performance such that the child was always training at maximal capacity. The children in the comparison group performed the tasks at a fixed level throughout the five-week period. The effect of the training was evaluated with a battery of neuropsychological tests, including the Span board task as the main outcome measure. In addition, parents and teachers rated the behaviour, of the children before and after the training. The long-term effects of the training were evaluated by performing the testing and rating again three months after the training had stopped.

The training group showed significant improvements compared to the comparison group on all tasks of executive function. The parent ratings showed significantly reduced numbers of ADHD symptoms related to inattention and hyperactivity/impulsivity. The improved performance on the Span board and the Digit span tasks and the reduction in symptoms was still present at follow-up.

The control group was not a true placebo group but underwent training at a lower level. This was meant to decrease the probability that the subjects and the parents/teachers would reveal which group the child belonged to. Furthermore, this low dose training would control for factors not related directly to WM training. These factors include improved attention and concentration on the task related to sitting in front of a computer and performing the same task for several days. Another factor is the aspect of being specifically encouraged and paid attention to by an adult for a long period of time.

3.4 Study IV

The ability to ignore distraction is central to WM (see section 1.6). This ability develops during childhood, but the neural basis underlying this development is largely unknown. A few previous studies have investigated the ability to ignore distraction in adults (de Fockert et al., 2004; Sakai et al., 2002) and indicated the importance of the DLPFC. No previous developmental study has investigated this ability. Furthermore, there is a lack of data showing the developmental changes in brain activity during the various phases of a WM task. Such data are necessary in order to establish which brain areas that are involved in each WM function involved in the task and to follow the development of those functions.

In Study IV, brain activity was measured in children and adults during the performance of a WM task that included distraction during the delay period. The analysis of brain activation data allowed us to evaluate both the effect of the distractor and the activity related to each WM phase and to look at effects of development on those data. According to previous studies, we hypothesized that adults would activate stronger than children in frontal and parietal areas (Klingberg et al., 2002a; Olesen et al., 2003) and that the effect of the distractor would be related to activity in the DLPFC (Sakai et al., 2002).

Each WM phase, including cue presentation, delay, distraction and selection, was analyzed separately. Brain activity underlying the main WM function related to each phase was analyzed in each group separately using one-sample *t*-tests. The most critical analyses were to identify group differences in WM-related brain activity for each phase. This was achieved using two-sample *t*-tests.

The results clearly showed the importance of the DLPFC to the ability to ignore distraction. Children were significantly more distracted than adults and activity in the DLPFC was found only in adults, during the delay. In children, the distractor affected activity in a region in the SFS that was related to the maintenance of relevant information. Regarding brain activity related to each WM phase, children and adults showed activity in similar areas during all phases, which is consistent with previous data showing that similar areas are activated during development of WM (Casey et al., 1995; Klingberg et al., 2002a; Nelson et al., 2000; Thomas et al., 1999).

Based on these findings we now have a better knowledge about the development of WM functions. First, maintenance of relevant information in the presence of distraction was related to activity in the DLPFC in adults but not in children. Second, in children the distractor was related to activity in the SFS, in a region that was important to maintenance of relevant information.

A possible explanation to these findings is based on the competition between the distractor and the target for neuronal processing resources. When a distractor appears it may compete with the task-relevant information for neuronal activity. If the internal representation of the relevant information is strong enough to resist the distractor, the distractor will “lose” this competition and the crucial WM-related activity remains devoted to the goal of the task. Possibly, the DLPFC is important for such stabilization of internal representations of information (see section 4.4). Further, in children the distractor may have “won” the competition for some of the neuronal activity, which was reflected as activity in the SFS. Since activity in this area was also important to maintenance of relevant information, the distractor may affect the internal representation of relevant information and thereby impair performance.

4 GENERAL DISCUSSION

4.1 Main findings of Study I-IV

In Study I and IV we found that development of WM was related to increased activity in frontal and parietal areas, which are known to be important for WM functions. Additionally, in Study I it was found that maturation of fronto-parietal white matter showed a similar developmental trend as brain activity in these frontal and parietal areas. The results from Study IV indicated that the changes in brain activity in frontal and parietal areas were related to maintenance of information in WM. Further, it was shown that the ability to ignore distraction included activity in the MFG which was present in adults but not in children. The lower ability in children was also related to a stronger effect of distraction on activity in the SFS.

Study II and III showed that WM training was related to increased WM capacity in both healthy adults (Study II) and children with impaired WM (Study III). The increase in WM capacity could be related to increased activity in frontal and parietal areas similar to the areas that were found to be important to development of WM. The effect of WM training generalized to non-trained tasks and included changes in behaviour in children with ADHD, which was seen as a decrease in symptoms of ADHD after training.

4.2 The fronto-parietal WM network

All imaging studies in this thesis consistently activated a fronto-parietal network of areas including the SFS, IPS and SPL. Additionally, the MFG was activated in Study II and IV (only in adults).

The importance of the PFC to WM functions was first shown by studies in patients (Owen et al., 1990) and non-human primates (Quintana and Fuster, 1993) with frontal lobe lesions and by single-unit recording in monkeys performing a WM task (Funahashi et al., 1989). Later, Friedman and Goldman-Rakic (1994) found that the parietal cortex coactivated with the DLPFC.

Today, there is substantial evidence implying central roles for the PFC and the parietal cortex for WM in humans (Cabeza and Nyberg, 2000; Klingberg et al., 1997; Naghavi and Nyberg, 2005; Smith and Jonides, 1998) and it has been confirmed that the areas work in parallel (Chafee and Goldman-Rakic, 2000). The importance of the PFC to WM functions is consistent with a general role of the PFC in the organization of temporal structures of action such as temporal organization of behaviour, speech and reasoning (Fuster, 2000; Wood and Grafman, 2003). Linking information over time is the most central WM function since information must be maintained on-line for short periods of time without any external sensory input.

The area specialized for spatial WM in monkeys is located in the monkey homologue of the human DLPFC i.e. the principal sulcus. Therefore, it was previously suggested that the DLPFC was essentially involved in maintenance of spatial information in WM. However, in humans the DLPFC may be responsible for maintenance of both object and spatial information (Curtis et al., 2004; McCarthy et al., 1994; Owen et al., 1998; Smith and Jonides, 1999). The area in the human brain that is comparable to the principal sulcus as an area specialized for spatial WM is possibly located in the SFS (Courtney et al., 1998). The location of this area, close to the premotor cortex, may explain why it took a long time to relate the activity to spatial WM rather than motor activity. The SFS activates specifically during the delay of spatial WM tasks, suggesting a function related to maintenance of spatial information (Courtney et al., 1998; Rowe and Passingham, 2001). Consistently, in Study IV the SFS was activated during the delay. In Study I and II it was not possible to separate activity related to a certain WM phase but activity in the SFS was present in both studies (Study II – unpublished data, main effect of WM-related activity).

Activity in the MFG was found in Study II and only in adults in Study IV. The reasons why the DLPFC is activated during the delay in some studies (Leung et al., 2002; McCarthy et al., 1994) and not in other (Manoach et al., 2003; Rowe et al., 2000) may include differences in task requirements (e.g. monitoring, sequence

representation) and task demand (e.g. high or low, with or without distraction). Our data suggest three primary functions for the DLPFC, which are supported by previous studies. First, the DLPFC was involved in actively maintaining the sequential relationship between stimuli (Study II), which possibly requires a high amount of monitoring (Petrides, 1991; Petrides, 2000). Second, it was required for active maintenance of information in the presence of distracting stimuli (Study IV) (Chao and Knight, 1998; D'Esposito et al., 1995; Miller et al., 1996). Third, the DLPFC was activated stronger on high demand trials (Study II, unpublished data comparing activity during performance on level 7 with activity during level 5 trials) (Cohen et al., 1997).

The pattern of connectivity of the SFS and DLPFC, respectively, with other cortical areas support the idea of functional specialization (Cavada and Goldman-Rakic, 1989; Petrides and Pandya, 1984; Petrides and Pandya, 1999). The SFS receives input from superior and medial parts of the parietal lobes that transfer visuo-spatial information (Petrides and Pandya, 1984), supporting a role in specific visuo-spatial WM functions. The major input to the DLPFC includes projections from the inferior parts of the parietal cortex and multimodal temporal areas (Petrides and Pandya, 1984; Petrides and Pandya, 1999) (see Figure 9 in (Petrides and Pandya, 1984)), consistent with a role in more general WM functions.

Taken together, our results support the existence of a fronto-parietal network underlying WM functions and the idea that there is a specialization of WM functions within the PFC. In section 4.5 I will discuss additional evidence for these findings and in section 4.6 I will bring up the idea that specialization of WM functions may also exist within the parietal cortex.

4.3 Which functions underlie improved WM?

We have shown that an increase in WM capacity, either during development (Study I and IV) or WM training (Study II), was related to changes in brain activity. In Study IV we could identify which changes in brain activity, related to the development of WM that were important for each WM phase. Thereby we got an indication on how specific WM functions were involved in the development of WM. However, in Study II, it was not possible to relate the changes in brain activity that occurred during training to specific WM functions.

In the next section I will discuss which functions that may underlie the training-related changes in activity by comparing the results in Study II to those in Study IV. In the section after that I will discuss in more detail, which specific functions that may be reflected in the activations found to be related to improved WM in both studies.

4.4 Which functions improve with WM training?

Several functions may candidate as underlying the improved WM after training presented in Study II and III. Increased capacity for maintenance of information is one candidate; improved accessibility of the maintained information is another. It is not possible to single out one candidate from the results in Study II since the fMRI data were analysed using a block design, which does not allow the separation of activity related to each function. However, the results from Study IV could give some hints

since these data were analysed using an event-related design. Thus, brain activity before training was compared to WM-related activity in children (i.e. low WM capacity) and activity after training was compared to WM-related activity in adults (i.e. high WM capacity).

In Study IV it was shown that high WM capacity (i.e. activity in adults) was related to activity in frontal and parietal areas during the delay. Analyses of group differences in activation showed that the delay was the only phase where the activity related to high WM capacity (adults) was significantly stronger than the activity representing low capacity (children). Thus, high WM capacity was related to activity during the delay in similar areas as those where increased activity was found after training (Table 1 and compare Study IV, Figure 4 to Study II, Figure 2 and 4). As we will see in section 4.5, this increased activity may reflect both a more stable representation of the information and increased capacity to maintain information. Decreased activity was mainly found in areas that were related to cue presentation and selection from WM (Table 1). The functions underlying cue presentation and selection could be related to attention, coding and retrieval of information and may become more efficient during training.

Table 1. Brain regions related to training and certain WM phases

Brain region		MNI coordinates			Training WM phase* effect
		x	y	z	
Cingulate sulcus	L	-3	6	45	Decrease Cue
	L	-4	6	48	
Inferior frontal sulcus	R	46	28	34	Decrease Selection
	R	42	30	24	
Middle frontal gyrus	R	36	21	18	Increase DelayD
	R	38	36	16	
Inferior/intra parietal cortex	R	46	-78	34	Increase Delay
	R	34	-70	24	
Inferior/intra parietal cortex	R	42	-57	45	Decrease Delay
	R	40	-48	58	
Inferior/intra parietal cortex	L	-52	-44	28	Increase DelayD
	L	-42	-46	36	
Intraparietal sulcus	R	18	-69	48	Decrease Selection
	R	14	-66	50	

* The regions were found in the analyses of WM main effect in adults (Study IV, Table 1), except those denoted with "D", which were found in the interaction analyses (Study IV, Table 3).

The effects of generalization suggest that increased WM capacity after training was related to an increase in domain-free WM functions. Indeed, the areas where changes in brain activity were found overlap with areas related to other higher cognitive functions (Duncan and Owen, 2000; Naghavi and Nyberg, 2005).

To summarize, it is possible that a more stable representation of the memorized information is created during training, which is more easily accessible and thereby improves selection of the appropriate representations.

It should be emphasized that the neural mechanisms underlying changes in brain activity that are related to differences in WM capacity may not be the same for development and training. However, until this has been investigated it may be relevant to compare these groups of people representing high and low WM capacity.

4.5 Maintenance and stabilization of internal representations of information in WM

One candidate function that may explain improvements in WM capacity related to both training (Study II and III) and development (Study I and IV) is the stabilization of internal representations in WM. This refers to the formation of a more robust neural basis for the representation of task-relevant information. Such a robust representation would be necessary when there is a high demand on the WM system e.g. during distraction and sequencing of information. It has been suggested that resistance to distraction is related to a stabilization of internal representations and it was suggested that executive processes underlie this effect (Sakai et al., 2002). In that study a visuo-spatial WM task was performed, which included a distractor task that appeared right before the response phase.

I will discuss how the findings in Study II and IV indicate that the same executive processing may be responsible for the improvements in WM capacity found in Study II, III and IV. To achieve this, I will try to identify which brain regions that may underlie maintenance of internal representations of information and which regions that may be involved in the stabilization of these representations. The discussion will be based on Table 2 and 3, which present comparisons between activations found in the frontal and parietal cortex in Study I, II and IV. These findings will be discussed in relation to the idea of stabilization of internal representations suggested by Sakai et al. (2002), why the areas presented in that study are included. In order to identify areas that are involved in maintenance of information, without distraction, I have also included results from Sakai & Passingham (2003) and Rowe et al. (2000). In Sakai the memorized information had to be recalled in both the forward and backward order. The data on brain activity related to forward trials is included in Table 2 and the activity related to backward trials is included in Table 3. The reason for this division is that backward trials require higher demand to hold the memory items than forward trials, which may reflect an increased stabilization of internal representations.

Table 2. Regions that may be involved in maintenance of spatial information in WM.

Brain region	Study	MNI coordinates		
		x	y	z
a. SFS				
	Olesen et al. (Study I)	-26	8	56
	Olesen et al. (Study IV, children)	-20	-12	56
	Sakai et al. (2003)	-26	-10	60
	Olesen et al. (Study IV, adults)	28	-8	50
	Sakai et al. (2002)	32	6	62
b. IPS				
	Olesen et al. (Study IV, adults)	40	-48	58
	Olesen et al. (Study IV, children)	26	-78	46
	Olesen et al. (Study I)	-36	-50	56
	Olesen et al. (Study IV, adults)	-36	-42	42
	Olesen et al. (Study IV, children)	-36	-60	58
	Rowe et al. (2000)	various regions*		
c. IPS/SPL				
	Olesen et al. (Study II, Experiment 2)	-4	-70	46
	Sakai et al. (2003)	-10	-70	54
	Olesen et al. (Study II, Experiment 2)	-22	-46	76
	Sakai et al. (2002)	18	-62	48
	Olesen et al. (Study II, Experiment 1)	18	-69	48

*The coordinates were reported in Talairach space and can not be directly compared to the data from this thesis, which were reported in MNI space.

Table 3. Regions that may be involved in stabilizing the internal representation of information in WM.

Brain region	Study	MNI coordinates		
		x	y	z
a. DLPFC				
	Olesen et al. (Study II, Experiment 2)	-26	22	56
	Sakai et al. (2002)	-44	54	22
	Sakai et al. (2003)	-42	34	26
	Olesen et al. (Study II, Experiment 1)	36	21	18
	Olesen et al. (Study IV, adults > children)	38	36	16
	Sakai et al. (2002)	40	46	22
	Sakai et al. (2003)	30	28	38
b. IPS				
	Olesen et al. (Study II, Experiment 2)	-52	-44	28
	Olesen et al. (Study IV, adults > children)	-42	-46	36
	Sakai et al. (2002)	-52	-40	40

Findings in the frontal cortex will be mentioned briefly since they have been discussed in more detail in section 4.2. The SFS was activated in both children and adults and in tasks with and without distraction (Table 2a). Activity in this region was related to development in Study I but not in Study IV. This inconsistency may be related to differences in age of the children. In Study I the participants were 8-18

years old and in Study IV the children were 13 years old. Possibly, development of WM during the time span 8-13 years involves activity in the SFS (Klingberg et al., 2002a). Activity in the SFS was not related to increased WM capacity during training. Activity in the MFG increased during training and was significantly stronger in adults than in children during the WM delay (Table 3a). The activity in the MFG was located close to an area that was reported to be involved in the stabilization of internal representations in WM (Sakai et al., 2002).

The functional specifications of the parietal areas were less evident. Brain activity was found in the IPS in both children and adults in various regions (Table 2b). These areas may be involved in both specific spatial (Rowe et al., 2000) and domain-free (Cohen et al., 1997; Coull and Frith, 1998) WM processes. However, a specific region in the IPS may be related to WM performance during distraction (Sakai et al., 2002). The areas where brain activity increased as an effect of training and development were located close to this region (Table 3b). Brain activity in other regions of the IPS/SPL (Table 2b) may reflect the capacity to maintain information (Todd and Marois, 2004).

These findings point out two factors that may underlie the improved WM capacity related to WM training: stabilization of internal representations and increased capacity to maintain information. On the other hand, the improved ability to resist distraction that comes with development was only related to stabilization of internal representations.

This summary of functional specialization within WM-related brain areas shows that information may be maintained in the SFS and various regions in the IPS/SPL (Table 4). In order to handle an increased demand on the system the neural representation of the information must be stabilized. The Sakai study (2002) showed that the increased stability may be accomplished by increasing the correlation of activity between regions in the SFS and IPS/SPL. The current summary support the idea brought up by the Sakai study that the DLPFC may be specialized for this function. Additionally, this summary suggests that specific neuronal populations within the IPS may be involved in this function (Table 4).

Table 4. Location of WM functions based on findings from study I, II and IV.

Function	Cortical region*	
	Frontal	Parietal
Maintenance of spatial information	SFS ^{I, II, IV}	IPS ^{I, IV} IPS/SPL ^{II, IV}
Stabilization of internal representation	DLPFC ^{II, IV}	IPS ^{II, IV}

* Study that presented activity in this region.

4.6 Functional specialization within the superior parietal lobe - High versus low demand

To add to the complexity of the neural basis for WM, a new analysis of training-related changes in brain activity in the parietal cortex showed that there was a functional specialization within the SPL. The new analysis showed that two different regions could be related to changes in performance during training on low and high demand trials, respectively.

In Study II, training-related changes in BOLD signal were presented by contrasting BOLD signal values from a frontal and a parietal voxel against day of scan. Figure 3b (section 3.2) shows the values presented in Study II including data for scan 6. The new analysis showed that the variation over time for BOLD signal values extracted from another parietal voxel was distinctly different from the values presented in Study II. The values were extracted from two closely located clusters based on their correlation with the same vector. However, the vector included scores from both low and high demand trials (see Study II, Figure 3b, “Grouped”). When the scores for these two trial types were plotted separately, two slightly different curves were seen (Figure 3a, section 3.2). The variation in these curves was similar to the variation between the two BOLD signal curves from the parietal cortex (Figure 4a). The curve representing scores at level 5 had a shape similar to the curve representing BOLD signal change in the anterior part of the SPL at location, x y z, [-22 -46 76] (Figure 4b). The shape of the curve representing level 7 was similar to the curve representing values extracted from the posterior part of the SPL at location [-4 -70 46] (Figure 4c).

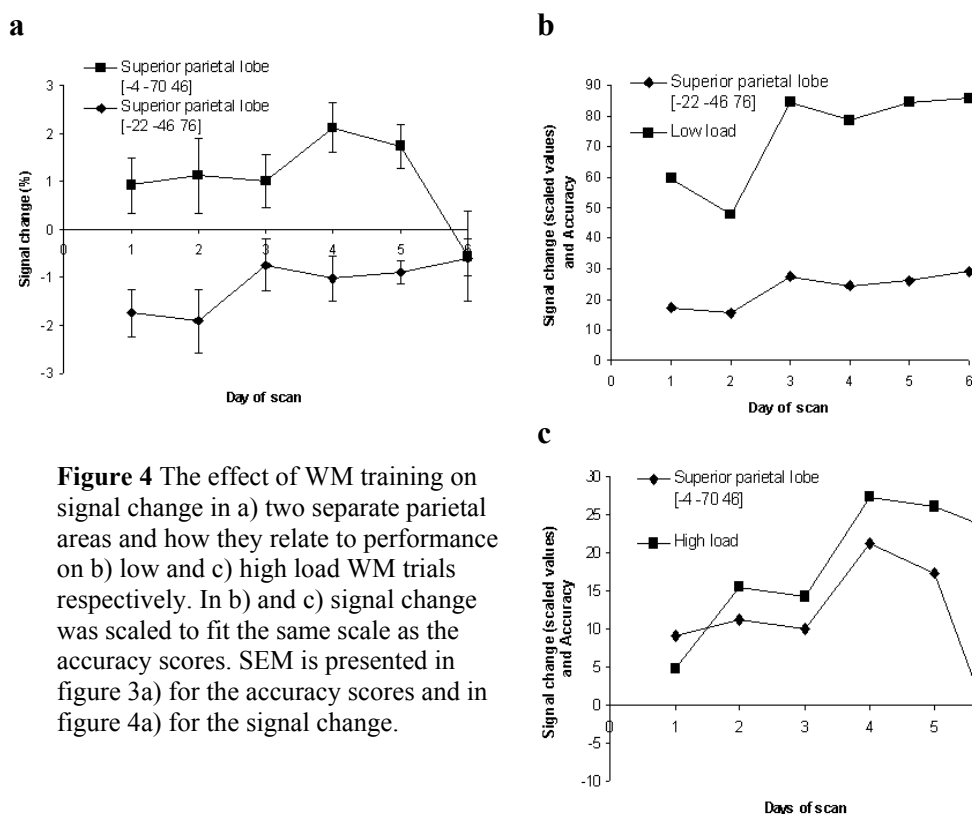


Figure 4 The effect of WM training on signal change in a) two separate parietal areas and how they relate to performance on b) low and c) high load WM trials respectively. In b) and c) signal change was scaled to fit the same scale as the accuracy scores. SEM is presented in figure 3a) for the accuracy scores and in figure 4a) for the signal change.

The idea that the posterior part of the SPL may be related to a more specialized WM function was supported by the results from Study IV. In an additional analysis it was found that adults activated significantly stronger than children (uncorrected for multiple comparisons, voxel-level statistics) during the delay, in the posterior SPL at location ([-8 -78 46]) close to the area that was presented in the training study ([-4 -70 46]). However, this was not the case for activity in more anterior parts of the SPL.

These new analyses indicate that there may be different clusters of neurons within the SPL that are important for low and high demands, respectively, on the WM system.

4.7 Increased activity during WM training

- Indication of brain plasticity

According to our hypothesis (section 1.13) we found that training of WM was related to improved performance and increased brain activity in task-related frontal and parietal areas. These changes in brain activity may reflect brain plasticity, i.e. the capacity to change cortical representations (Black, 2000). I will now discuss what may be the neural basis for this plasticity, possibly underlying the improvements in WM capacity in Study II and III. The neural mechanisms underlying improved WM capacity during development were discussed in the introduction, section 1.11.

4.8 Possible neural mechanisms underlying the effects of WM training

The most commonly mentioned factor underlying cortical reorganization in the adult brain is modifications of connections, through synaptogenesis and synaptic plasticity (i.e. the ability of neurons to modulate the strength and structure of their synaptic connections (Black, 2000)), and sprouting of axon collaterals (Bavelier and Neville, 2002; Buonomano and Merzenich, 1998; Gilbert, 1998; Kaas, 1991). These modifications may enhance the horizontal circuitry, which refers to the lateral axons of pyramidal cells extending within and between functional columns (Donoghue, 1995). Changes in the horizontal circuitry have mainly been studied in the visual cortex, but similar circuitries may be found in other cortical areas (Donoghue, 1995; Sanes and Donoghue, 2000) including the PFC (Gonzalez-Burgos et al., 2000).

The training-related changes in brain activity (Study II) and WM capacity (Study II and III) presented in this thesis may reflect enhancement of horizontal circuitries. First, changes in the horizontal circuitry are activity-dependent (Donoghue, 1995; Zito and Svoboda, 2002). Second, changes in the long-range horizontal connectivity take place over weeks or months (Gilbert, 1998). Third, motor learning, rather than passive movements, has been related to an increase in the number of synapses per neuron in the rat motor cortex (Kleim et al., 1996) and cerebellum (Kleim et al., 1997). Importantly, in a study by Kleim et al. (1997) the effect of training on synaptic density persisted for at least one month after the training had stopped. Furthermore, the communication between task-related areas may become enhanced during training. One evidence for this is that an increase in actions potentials e.g. as an effect of synaptogenesis, may indirectly increase myelinogenesis (Demerens et al., 1996).

All the previous studies on brain reorganization have focused on primary and secondary sensory and motor areas. Possibly, these findings extend to higher order association cortex. However, until this is confirmed it should be mentioned that there could be differences in the plasticity of lower and higher order cortical areas.

4.9 Long-term skill learning and brain activity

- How unique are our findings?

The previous literature on skill learning is dominated by studies on motor and perceptual skill learning and they have focused on training that takes place for less than a day. Furthermore, this previous literature has not aimed at increasing the

capacity of the function underlying task performance. Instead, the focus has been on an increased efficiency in the execution of a task.

In the training studies in this thesis (Study II and III) the aim was to increase WM capacity by providing long-term training on various WM tasks. Importantly, the difficulty level during training was adapted to each individual's performance. The idea was that the most efficient training effect on capacity would be seen if training was performed on the maximum level for each individual. We found training-related changes in brain activity in WM-related areas that were involved in the task before training. Thus, the results supported our hypothesis (section 1.13) that WM training would involve changes in an already existing neural network.

In order to compare our results with other studies, a review of the previous publications, searchable in PubMed, was performed (also mentioned in section 1.13). The review included studies on long-term (> 1day) skill learning in healthy adults where the training effect on brain activity was analysed. Further, studies were included if scanning took place more than one time in each subject in order to compare brain activity after training with before training.

Twenty-seven publications met these criteria. Only four of these publications (including Study II) used an adaptive training paradigm (Golestani and Zatorre, 2004; Olesen et al., 2004; Schiltz et al., 1999; Schiltz et al., 2001). Of the 27 publications, 4 included cognitive skill learning (Hempel et al., 2004; Little et al., 2004; Olesen et al., 2004; Qin et al., 2003), 11 included perceptual (Callan et al., 2003; Furmanski et al., 2004; Golestani and Zatorre, 2004; Kassubek et al., 2001; Kourtzi et al., 2005; Lee et al., 2003; Poldrack et al., 1998; Poldrack and Gabrieli, 2001; Schiltz et al., 1999; Schiltz et al., 2001; Wang et al., 2003) and 12 included motor skill learning (De Weerd et al., 2003; Debaere et al., 2004; Draganski et al., 2004; Floyer-Lea and Matthews, 2005; Haier et al., 1992; Hlustik et al., 2004; Karni et al., 1995; Parsons et al., 2005; Poldrack et al., 2005; Puttemans et al., 2005; Tracy et al., 2003; Van Der Graaf et al., 2004). The effects of skill learning on brain activity were inconsistent but it was possible to extract a general pattern. It was found that the training effect depended on the function that was trained. Motor skill learning was related to increased activity in, or increased extent of, the motor cortex (6 out of 12 studies) (Debaere et al., 2004; Floyer-Lea and Matthews, 2005; Hlustik et al., 2004; Karni et al., 1995; Puttemans et al., 2005; Van Der Graaf et al., 2004). Visual perceptual skill learning was related to decreased activity in visual cortex (6 out of 7) (Kassubek et al., 2001; Kourtzi et al., 2005; Poldrack et al., 1998; Poldrack and Gabrieli, 2001; Schiltz et al., 1999; Schiltz et al., 2001). However, more complex perceptual skill learning, which involved verbal speech processing and acoustic-phonetic processing, was related to increased activity in speech-related areas (3 out of 4) (Callan et al., 2003; Golestani and Zatorre, 2004; Wang et al., 2003). Cognitive skill learning involved changes in brain activity in the PFC (4 out of 4) (Hempel et al., 2004; Little et al., 2004; Olesen et al., 2004; Qin et al., 2003) and PPC (3 out of 4) (Hempel et al., 2004; Little et al., 2004; Olesen et al., 2004).

Possibly, the inconsistencies in the effects of training on brain activity are related to differences in the neural mechanisms underlying the function that is trained. Decreased activity in the visual cortex may be explained by a reduced number of neurons that are more narrowly tuned and shows increased selectivity to the task-

related information (Schoups et al., 2001). On the other hand, neurons in motor cortex involved in skill learning, may work by building up a specific motor representation of the information that is to be learned, which may require more activity (Karni et al., 1995). Neurons in multi-modal areas, such as those involved in WM training in this thesis, may work by increasing the amount of information that can be maintained, or attended to, and by stabilizing the representation of the information (see further section 4.5).

4.10 The visual system and spatial attention in relation to WM

Neural mechanisms devoted to visual or oculomotor functions and spatial attention are hard to separate from WM systems since these functions often occur simultaneously. I will now discuss how these systems may relate to each other and to the findings in this thesis.

The process of maintaining information on-line in WM almost always aligns with the direction of spatial attention. Possibly, the most efficient way for the brain to match such overlapping functions is to recruit the same areas for both processes. Consistently, the functional areas related to spatial WM and spatial attention overlap in a fronto-parietal network (Corbetta et al., 2002; LaBar et al., 1999). The same kind of reasoning may apply to the direction of gaze and spatial attention and there is an overlap between the areas included in the network controlling gaze direction and the network for spatial attention (Corbetta et al., 1998).

It is hard to separate the FEF, responsible for saccadic eye movements, from the SFS based on activations presented in analyses of fMRI data since the spatial resolution is too low (about 2 mm (Jezzard and Clare, 2001)). It is currently unknown whether there actually exist two separate brain regions, or whether there is a functional overlap within one region. It may be that the neurons involved in saccadic eye movements and the neurons responsible for maintenance of spatial information in WM are intermixed in the same brain region. The FEF codes spatial information and activates regardless of eye movements (Astafiev et al., 2003) implying a role in spatially guided attention, driven by internal representations of goal-states. Generally, when discussing brain function, it is important to acknowledge that there is probably not a one-to-one association of function and brain area (Mesulam, 1990), rather each region in the brain may support several functions.

The frontal and parietal activations that were found in this thesis probably reflect both spatial selective attention and spatial WM. Activity related to visual and oculomotor functions has been subtracted out since each control task was designed to include the same amount of such activity as the WM tasks.

4.11 The caudate nucleus and WM

Activity in the caudate nucleus was related to the development of WM in Study I and to training of WM in Study II. The striatum, and specifically the caudate nucleus, is known to be involved in spatial WM (Levy et al., 1997). Patients with Parkinson's disease, which affects essentially the striatum, perform poorly on WM tasks (Le Bras et al., 1999). Additionally, cognitive skill learning has previously been related to increased activity in the caudate nucleus (Poldrack et al., 1999; Schiltz et al., 2001).

In this thesis, activity in the caudate nucleus co-occurred with activity in the PFC, which may reflect the heavy connections between these areas (Yeterian and Pandya, 1991). The role of the caudate in skill learning and development of WM is unclear. It may be related to spatially mediated motor preparation i.e. the formulation of a motor response based on a spatially coded representation of the information (Postle and D'Esposito, 1999; Postle and D'Esposito, 2003). Possibly, this function was more involved in Study I and II where the information was presented sequentially, than in Study IV where all cues were presented at the same time and 50% of the trials did not require any response. Thus, during development and training of WM the sensory-motor transformation of information in WM may become more efficient.

4.12 Imaging development

The main concern when applying fMRI to paediatric populations and comparing the results to adult data has been the motion artefacts and the differences in brain size and performance (Poldrack et al., 2002). These concerns, and how they were approached in Study I and IV, will be discussed.

Brain volume does not change significantly after age 5 years (Giedd et al., 1996; Reiss et al., 1996). Later in childhood it is mainly the shape and structure of the brain that changes. Grey matter density decreases after age 12 years (Giedd, 2004) and white matter increases throughout childhood and adolescence (Giedd, 2004). The resulting differences in localization may be below the resolution of fMRI. This is supported by studies showing that it is feasible to normalize children and adult brains to a common template and to compare brain activations between age groups (Burgund et al., 2002; Kang et al., 2003). Consistently, the same template was used for children and adults in Study I and IV.

Children may move their heads more than adults during scanning why it is important to control for head motion to eliminate the chance that some of the group differences in activity may be related to movement. For the studies in this thesis, images were excluded if movement in any direction exceeded 2 mm. Further, in Study I activity related to motion artifacts was controlled for by including the movement parameters as regressors of no interest in the GLM. In Study IV movement-related variance was removed using the Unwarp toolbox in SPM2 (Andersson et al., 2001).

Performance and differences in load on the WM system must also be considered when comparing imaging data from children and adults. Variations in brain activity between individuals may reflect both differences in performance and load on the WM system. Regarding WM, high performance (Curtis et al., 2004; Pessoa et al., 2002) and high load (Rypma et al., 1999; Vannini et al., 2004) has been related to high activity in frontal and parietal areas. These previous studies do not show whether the direction of the difference (high activity related to high load and high performance) may be different when brain development underlies some of the variability. Nevertheless, in developmental imaging studies it is important to exclude that the differences in brain activity are not only related to differences in load or performance. However, some of the performance-related activity may be related to development (Durstun et al., 2002). For example, in Study IV, there was no correlation between brain activity in the areas where significant group differences were found and performance during scanning

within each group. Rather, the correlation was driven by group differences in activity and performance, indicating that any difference in activity related to performance could be explained by development.

To conclude, when we study different age groups it is important to remember that differences in performance may include variation related to development. Removing this variability from the analyses of imaging data (e.g. by including performance scores as a factor of no interest in the design matrix) could have the effect that activations that are important for development are missed.

4.13 Generalization of the effects of WM training

In this thesis there are three separate studies on the effects of WM training on performance: Study II, which includes two separate studies, Experiment 1 and 2, and Study III. The training effects on performance will be discussed and compared between the studies. It is important to remember that the number of subjects in Study II is too small to draw any inferences to the general population regarding the performance data. Therefore, this is only a visual presentation and comparison of the training effects and not a statistical analysis.

Figure 5 presents the training effects on visuo-spatial WM performance (Figure 5a) and verbal WM performance (Figure 5b) for adults (Experiment 2) and children. Training effects are presented as the difference between scores before training and scores after training and at follow-up. The data for adults are compared to test-retest performance for adults who did not participate in WM training. The control group for children participated in low dose WM training (see Study III, “Intervention”).

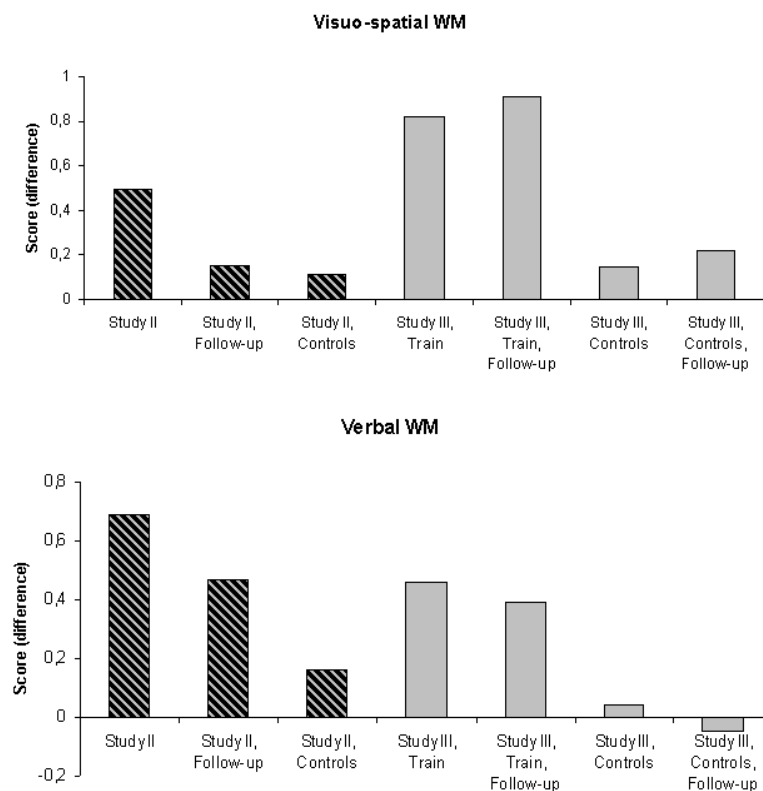


Figure 5 The effect of WM training on performance in children with ADHD and adults on a) visuo-spatial and b) verbal WM tasks.

Children improved more than adults on the visuo-spatial WM task and adults improved more on the verbal WM task. The improvements at follow-up were stronger in children than in adults. These long-term effects suggest that WM training may have a stronger impact on every-day life activities in children with impaired WM than in adults with normal WM.

Even when the training included only visuo-spatial WM tasks (Study II, Experiment 2), there was an improvement in verbal WM performance (Figure 5b). This may reflect that some of the activity related to verbal and visuo-spatial WM, respectively, is located in similar brain areas (Cabeza and Nyberg, 2000). However, the effects of generalization may be stronger when the training includes both visuo-spatial and verbal WM tasks. Considering that the neuronal input from separate domains may be intermixed in the domain-general areas, it is possible that the domain-general areas are more efficiently stimulated when there is input from different domains, rather than input from only one type of domain.

These differences in the effects of generalization related to WM training may be due to differences between children and adults or between people with and without deficient WM or both.

4.14 Ideas for future studies

This thesis has contributed with important new findings on the latent capacity of the human brain, which was targeted with WM training. These data are only the first step towards the unravelling of the neural basis for cognitive skill training. Further approaches may include: 1) identifying which WM functions that underlie the training effects and 2) distinguish whether the increased activity reflects increased synaptic firing in the same neuronal clusters as before training or an increase in the extent of cortex that is recruited. Additionally, studies of connectivity between brain regions could give a more detailed picture of the relationship between areas in the WM network and how these relationships change during training and development.

It would be clinically relevant to investigate whether there is a potential for WM training to be used as a treatment for other groups of people with impaired WM such as patients with Schizophrenia (Karatekin and Asarnow, 1998), Stroke patients (Sachdev et al., 2004) and old people (Hester et al., 2004). Cognitive training has been shown to increase WM capacity and task-related brain activity in patients with schizophrenia (Wexler et al., 2000; Wykes et al., 2002). It is possible that in patients, WM training results in a normalization of brain function, i.e. after training, the brain activation pattern may look more like that in healthy individuals than before training.

We have attempted to integrate data on behavioural measures with data on brain function and structure to get a deeper understanding of the neurobiology of WM. The next step could be to integrate these data with yet another level of detail; the behaviour of neurons in computational models of WM. Possible targets could be to investigate which changes in neuronal network models that are necessary in order to get the changes in brain activity that are related to the development of WM.

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