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Neural Mechanisms Determining the Performance on Visuospatial Working Memory Tasks

Biophysical Modeling, Functional MR Imaging and EEG

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Abstract

Visuospatial working memory (vsWM) is the ability to temporarily retain goal-relevant visuospatial information in memory. It is a key cognitive function related to general intelligence, and it improves throughout childhood and through WM training. Information is maintained in vsWM through persistent neuronal activity in a fronto-parietal network that consists of the intraparietal sulcus (IPS) and the frontal eye field (FEF). This network is regulated by the dorsolateral prefrontal cortex (dlPFC).

The features of brain structure and activity that regulate the access to and storage capacity of visuospatial WM (vsWM) are still unknown. The aim of my doctoral work has been to find such features by combining a biophysically based model of vsWM activity with functional MRI (fMRI) and EEG experiments.

In study I, we combined modeling and fMRI and showed that stronger fronto-parietal synaptic connections result in developmental increases in brain activity and in improved vsWM during development. This causal relationship was established by ruling out other previously suggested mechanisms, such as myelination or synaptic pruning,

In study II, we combined modeling and EEG to further explore the connectivity of the network. We showed that FEF→IPS connections are stronger than IPS→FEF connections, and that stimuli enter IPS. This arrangement of connections prevents distracting stimuli from being stored.

Study III was a theoretical study showing that errors in measurements of the amplitude of brain activity affect the estimation of effective connection strength.

In study IV, we analyzed EEG data from WM training in children with epilepsy. Improvements on the trained task were accompanied by increased frontal and parietal signal power, but not fronto-parietal coherence. This indicates that local changes in FEF and IPS could underlie improvements on the trained task.

dlPFC is important for the performance on a large variety of cognitive tasks. In study V, we combined modeling with fMRI to test the hypothesis that dlPFC improves vsWM capacity by providing stabilizing excitatory inputs to IPS, and that dlPFC filters distracters by specifically lowering the capacity of neurons storing distracters. fMRI data confirmed the model hypothesis. We further showed that a dysfunctional dlPFC could explain the link between vsWM capacity and distractibility, as is found in ADHD. The model suggests that dlPFC carries out its multifaceted behavior not by performing advanced calculations itself, but by providing bias signals that control operations performed in the regions it connects to.

A specific aim of this thesis has been to describe the mechanistic model in a way that is accessible to people without a modeling background.

Sammanfattning på svenska

Visuella rumsarbetsminnet (vrAM) är förmågan att temporärt hålla målrelevant visuell rumsinformation i minnet. Det är en nyckelfunktion som är relaterad till generell intelligens, och det förbättras under uppväxten samt genom träning. Information hålls i vrAM genom ihållande neuronal aktivitet i ett nätverk i pann- pch hjässloberna bestående av sulcus intraparietalis (IPS) och det frontala ögonfältet (eng: frontal eye field; FEF). Nätverket regleras dessutom av dorsolaterala prefrontalkortex (dlPFC).

Det är fortfarande okänt vilka egenskaper hos hjärnans struktur och aktivitet som reglerar tillträdet till och lagringskapaciteten i visuella rumsarbetsminnet (vrAM). Målet med mitt doktorsarbete har varit att finns sådana egenskaper genom att kombinera en biofysiskt baserad modell av vrAM-aktivitet med experiment med funktionell MRI (fMRI) och EEG.

Studie I kombinerade modellering och fMRI och visade att starkare synaptiska kopplingar mellan pann- och hjässloberna orsakar ökningar av hjärnaktivitet och förbättrat vrAM under uppväxten. Detta orsakssamband etablerades genom att utesluta tidigare föreslagna mekanismer som myelinering eller synaptisk gallring.

Studie II kombinerade modellering och EEG för att vidare utforska kopplingarna i nätverket. Vi visade att FEF→IPS-kopplingarna är starkare än IPS→FEF-kopplingarna samt att information kommer in i nätverket via IPS. Detta kopplingsmönster förhindrar att oviktig och distraherande information lagras.

Studie III var en teoretisk studie som visade att mätfel i aktivitetsnivå har påverkan på uppskattningar av effektiv kopplingsstyrka.

Studie IV analyserade EEG-data från AM-träning hos barn med epilepsi. Förbättringar på den tränade uppgiften åtföljdes av ökad fronto-parietal signaleffekt, men inte koherens. Detta antyder att de testförbättringarna på den tränade uppgiften skulle kunna vara orsakade av lokala förändringar i FEF och IPS.

dlPFC är viktigt för prestationen på ett stort antal kognitiva uppgifter. Studie V kombinerade modellering med fMRI för att testa hypotesen att dlPFC förbättrar vrAM-kapaciteten genom att tillföra stabiliserande excitatoriska strömmar in till IPS, samt att dlPFC filtrerar distraherande stimuli genom att specifikt sänka vsAM-kapaciteten hos neuroner i IPS som kodar för distraktorer. fMRI bekräftade modellhypotesen. Vi visade vidare att ett dåligt fungerande dlPFC förklarar kopplingen mellan vrAM-kapacitet och distraktibilitet, såsom återfinnes i ADHD. Modellen föreslår att dlPFC utför sitt mångfacetterade beteende inte genom att själv genomföra avancerade beräkningar, utan genom att tillföra styrsignaler som kontrollerar motsvarande processer i de regioner det kopplar till.

Ett specifikt mål med denna avhandling har varit att beskriva den mekanistiska modellen på ett sätt som är tillgängligt för personer utan modellerings-bakgrund.

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Studies

Studies included in this thesis

I. Edin F., Macoveanu J., Olesen P.J., Tegnér J., Klingberg T. (2007) Stronger synaptic connectivity as a mechanism behind development of working memory-related brain activity during childhood. *Journal of Cognitive Neuroscience* 19:750-60.

II. Edin F., Klingberg T., Stödberg T., Tegnér J. (2007) Fronto-parietal connection asymmetry regulates working memory distractibility. *Journal of Integrative Neuroscience,* to appear in Dec.

III. Edin F. Scaling errors in measures of brain activity cause erroneous estimates of neural connectivity. *Under revision.*

IV. Edin F., Stödberg T., Persson R., Hedman P., Tegnér J., Dahlin M., Westerberg H., Klingberg T. Alpha synchronization after training of visuospatial working memory in patients with epilepsy. *Manuscript*.

V. Edin F., Johansson P., McNab F., Klingberg T., Tegnér J., Compte A. Flexible Prefrontal Bias Signals Regulate Capacity and Access to Working Memory. *Manuscript*.

Studies not included in this thesis

1. Edin F., Huss M. Simulating epilepsy on complex networks to infer cortical connectivity. *Manuscript*
2. Edin F., Machens C.K., Schütze H., Herz A.V.M. (2004) Searching for optimal sensory signals: Iterative stimulus reconstruction in closed-loop experiments. *Journal of Computational Neuroscience* 17:39-48.
3. Englund M., Bjurling M., Edin F., Hyllienmark L., Brismar T. (2004) Hypoxic excitability changes and sodium currents in hippocampal CA1 neurons. *Cellular and Molecular Neurobiology* 24:685-94.

List of abbreviations

ADHD:	attention-deficit hyperactivity disorder
ANOVA:	analysis of variance
BOLD:	blood-oxygenation level dependent
dlPFC:	dorsolateral prefrontal cortex
DR:	delayed response
DTF:	directed transfer function
EEG:	electroencephalogram
FEF:	frontal eye field
fMRI:	functional magnetic resonance imaging
IPS:	intraparietal sulcus
PFC:	prefrontal cortex
SFS:	superior frontal sulcus
STM:	short-term memory
vs:	visuospatial
WM:	working memory

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Introduction

Visuospatial working memory (vsWM) and the aim of this thesis

Visuospatial working memory/short-term memory (vsWM/STM) is the temporary retention of goal-relevant visuospatial information through persistent brain activity[2] (Goldman-Rakic, 1995). vsWM is a basic human cognitive function. Every time you dial a phone number, make up a mental list of things to do, picture the route you need to take to get to an important meeting, or perform any other similar activity, you need to transiently store information. Your brain is able to perform these tasks because there are neurons that are active during the time that you keep things in memory. The brain loci of the persistent activity that enables retention of information in vsWM are most likely the intraparietal sulcus (IPS; Todd and Marois, 2004, Xu and Chun, 2006), a parietal brain region, and the frontal eye field (FEF; Courtney et al., 1998, Curtis, 2006), a frontal region.

A basic feature of the vsWM brain network is its limited capacity. vsWM capacity is the maximum number of memories that can be stored. Generally, only around 4 memories can be held in vsWM simultaneously (Cowan, 2001, Todd and Marois, 2004, Xu and Chun, 2006), although the exact number depends on the method of measurement and the task performed. Because of the limited capacity, it is very important to only allow goal-relevant information to enter the fronto-parietal vsWM retention network (Vogel et al., 2005). Several factors other than pure fronto-parietal memory capacity are inextricably linked to the performance on vsWM tasks (Miyake and Shah, 1999). The single most important of these factors seems to be controlled attention [3] reflected through activity in brain regions such as the dorsolateral prefrontal cortex (dlPFC; Miller and Cohen, 2001, dlPFC; Kane and Engle, 2002), and controlled attention is often included in the concept of working memory. Often, researchers distinguish between vsSTM and vsWM (Engle et al., 1999, Kane and Engle, 2002), where the latter concept includes attentional control signals from dlPFC to the memory regions, and the former does not.

vsWM is not only important for its own sake, but has also been associated with many other cognitive functions, most notably general intelligence[4] (Engle et al., 1999). This is possibly due to activity in the dlPFC region, which is found in a wide range of cognitive tasks (Duncan and Owen, 2000). In addition, vsWM is involved in several of the cognitive deficits associated with diagnoses such as attention-deficit hyperactivity disorder (ADHD; Westerberg et al., 2004). This serves as a further motivation to study vsWM.

vsWM is not static and not the same in every person. vsWM improves during childhood, peaks during adulthood, and deteriorates during old age (Jenkins et al., 1999, Fry and Hale, 2000, Klingberg et al., 2002, Gathercole et al., 2004). Thus, there is plasticity in the brain to which it can be linked. vsWM can also be trained, and

[2] Brain activity: Cells in the brain send out electrical impulses called action potentials or spikes. Activity is commonly defined as the number of impulses per second, the firing rate. Neural activity defined this way is measured indirectly with functional MRI or EEG (see *Discussion*). See methods for their relationship to neuronal firing rate.

[3] "Controlled attention" refers to the ability to voluntarily focus attention, as opposed to when salient stimuli in the surroundings grab your attention ("bottom-up attention"). Synonyms are "executive attention", "top-down attention" or "cortical control".

[4] A weighted average of the scores on a standardized battery of cognitive tests. IQ is an age-corrected measure of the general intelligence of a person.

vsWM training is used to alleviate symptoms in children with ADHD, among others (Olesen et al., 2004, Klingberg et al., 2005, Westerberg et al., 2007).

It is important to understand the neural mechanisms behind vsWM for the theoretical and medical reasons listed above as well as for technological reasons (How are brain-inspired computers built?). In the Developmental Cognitive Neuroscience group at Karolinska Institutet research has focused on understanding the neural basis of the development of WM in healthy children and children with ADHD. The second major research topic has been the development of training methods that improve WM. During my doctoral training, I have implemented and further developed an existing mechanistic model[5] in order to understand the neural changes that take place during development and training as well as other neuronal factors that regulate WM performance and brain activity. My main aim has been to use this model to predict and interpret experimentally observed differences such as those found between children and adults. At the same time, the behavioral and brain activity data that the Developmental Cognitive Neuroscience group has analyzed have led to improvements of the model, which now incorporates more of what is currently known about the vsWM brain network. Perhaps due to the type of data available in the literature and the experimental techniques used, functional magnetic resonance imaging (fMRI) and EEG, both of which have relatively low spatial resolution, the studies have largely investigated the effect of brain connectivity on global brain activity rather than the effect of various intracellular or neuromodula-tory factors on finer aspects of activity. In order to compare to experimental data, the model was developed to include several brain regions, whereas most previous models have included only one.

The approach used in this thesis to study vsWM is novel in several respects. It is one of the first attempts to combine mechanistic modeling of vsWM with in-house measurements of human global brain activity and task performance to learn and make inferences about basic mechanisms determining vsWM in humans (for similar approaches, see also Husain et al., 2004, Fusi et al., 2007). This approach has allowed an interchange between model and data that has been beneficial both for making inferences from data and for developing the model. The model was expanded in three steps: (1) to incorporate several regions for memory retention so that factors such as myelination could be studied, (2) to represent multiple memories and (3) to include a simple model of dlPFC activity in a first attempt to understand top-down[6] attentional modulation of retention activity and its consequences for individual differences in vsWM capacity and distractibility[7].

Specific aims of the thesis

Study I: We wanted to determine the neural basis of vsWM development during childhood by making model predictions of neural activity that we tested with fMRI.

[5] To understand what a mechanistic model is, note that a flight simulator is a type of mechanistic model that describes air flight in terms of the laws of physics. With a flight simulator, it is possible to study a system in a perfectly controlled environment. The researcher knows exactly all the parameters in the system. It is also possible to perform tests that could not have been done in real life, such as various ways of crashing the plane. The value of this technique of course depends on the quality of the simulator/model, which is measured by how well it can predict similar situations in real life.

[6] Top-down: from higher to lower regions in the cortical hierarchy. dlPFC is the highest region of those studied in this thesis (Felleman and Van Essen, 1991).

[7] The degree of memory degradation due to the presentation of irrelevant and distracting stimuli (distracters).

We concluded that stronger fronto-parietal synaptic[8] connections underlie vsWM improvements.

Study II: Here, we wanted to understand whether synaptic connections between IPS and FEF[9] are equally strong or not, as well as the main route of entry of stimuli into the vsWM network. We also wanted to investigate the functional consequences of asymmetry on distracter processing. We concluded that frontal connections are stronger than parietal and that stimuli primarily enter IPS. This structural arrangement improves the stability of vsWM against distracting stimuli.

Study III: I explored a source of errors in estimates of inter-regional effective connectivity[10]. I found that estimates can be highly inaccurate if the signal strength from different regions varies for reasons other than variation in brain activity. This is a problem that occurs both in fMRI and EEG.

Study IV: We explored the neural basis of vsWM training with EEG. Training increased frontal and parietal α band power[11] and improved performance on the tested task. It is possible that improved task performance is caused by factors inside each region of the fronto-parietal vsWM network.

Study V: We used mechanistic modeling to test a conjecture for a general mechanism where dlPFC modulates vsWM (and presumably other cognitive functions) by sending bias signals to target regions, in this case IPS. We also wanted to explore whether this mechanism explains the relationship between vsWM performance and distractibility, as is, e.g., seen in ADHD (Westerberg et al., 2004, Keage et al., 2006). We found fMRI support for this mechanism and that it can explain the association between vsWM and distractibility. We developed a set of two simple and intuitive equations for vsWM capacity that explains how dlPFC transmits flexible and task-dependent bias signals that up-regulates the capacity for storing memories and down-regulate the capacity for storing distracters.

Finally, it has been my aim during the writing of this thesis to describe the model in an accessible way and clearly point out how I have related the model to experimental data. Mechanistic modeling is one of the main techniques of cognitive neuroscience, but the research methodology and often also the aims are relatively different from research performed with techniques such as fMRI. This has made the communication of modeling results difficult. Sometimes, my explanations of model dynamics have led to arguments that are quite involved. However, I hope that readers that are not themselves modelers but have an interest in the neural mechanisms underlying vsWM activity and task performance will still feel that the time spent learning about the model has improved their understanding of vsWM.

vsWM definition and the visuospatial delayed response (vsDR) task

Despite the long history of WM research, no definition of WM is generally agreed upon (Miyake and Shah, 1999). In their book "Models of working memory", editors Miyake and Shah list a number of models, metaphors and definitions of working

[8] A synapse forms the connection between two neurons and can be excitatory or inhibitory. A synapse transforms activity (action potentials) from the presynaptic (sending) cell into currents that are fed into the receiving (postsynaptic) cell.

[9] Note that the term superior frontal sulcus (SFS) is used in the studies in place of the term FEF. In both cases, the two denote the same, the frontal memory region that activates during vsWM. See also the *Functional anatomy of vsWM* section.

[10] Effective connectivity: the net connection strength from one region or cell to another.

[11] α band power: amplitude of oscillations with frequencies between 8 – 10 Hz.

Table 1. Different theories of WM.[a]

Proponent	Main content of theory
Baddeley	Temporary maintenance in modality-specific stores and manipulation of information through the extraction of information to a shared processor.
Goldman-Rakic	Maintenance of task-relevant information through persistent neural activity.
Olton	The ability of an animal (usually a rodent) to keep track of its location in space by remembering where it has been.
Engle/Cowan	Temporary activation of long-term memory in domain-specific stores that requires domain-general attentional support.
Ericsson	Maintenance via the activation of quickly changing long-term representation (long-term working memory), which enable the association of items of information to facilitate memory.

a) As listed in Miyake and Shah (1999), but also in Olton (1977) and Goldman-Rakic (1995).

memory. The different descriptions of WM expressed by the scientists contributing to the book all have in common that

- WM is the temporary maintenance of task-relevant information.

Table 1 lists some theories of WM and their proponents. One of the reasons for the differences in the definitions of vsWM is that each scientist studies very different WM tasks and emphasizes different aspects of these tasks. Thus, whereas scientists that study the neurophysiology of WM in monkeys have primarily investigated basic mechanisms of information retention, the main goal of many cognitive psychologists has been to study individual differences. Since the performance on a WM task depends on other factors than the basic mechanism of maintenance, the scientists consequently view WM differently. Yet other scientists study memoranda for which another type of memory, long-term memory [12], is an important factor for task performance, and therefore see WM as a function of long-term memory.

Another reason why no consensus exists about WM is that up until recently, neural activity data related to WM and especially individual differences in WM have been very scarce (Miyake and Shah, 1999). Thus, theoretical development has mostly been based on task performance data, which makes the theoretical constructs hard to map to neural activity patterns. However, Engle and others have developed a view of vsWM as consisting of a maintenance component and a controlled attention component, which is thought to be instantiated in the brain as modulation of memory brain regions via top-down bias signals from dlPFC (Miller and Cohen, 2001). The controlled attention component is suggested to operate when various non-automated operations need to be performed (Engle et al., 1999, Kane and Engle, 2002, Kane et al., 2007). As I discuss below, this division corresponds relatively well to what has recently been learnt about activity in different brain areas during the performance of the delayed response (vsDR) task (Figure 1), arguably the most popular task for vsWM research in both humans and monkeys (Fuster, 2001) and the task used in the studies in this thesis. Therefore, the studies in this thesis are based on a definition of

[12] Long-term memory: memories that are stored in the synaptic or intra-cellular molecular structure of the brain for hours or longer.

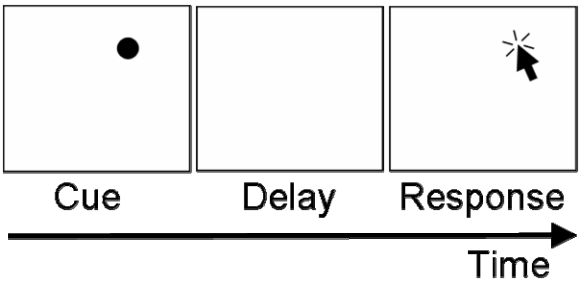

Figure 1. The visuospatial delayed response (vsDR) task. In this version of the task, a cue dot is presented on a computer screen. The location of the dot is supposed to be reproduced after the end of the delay period by clicking with a mouse pointer at the location of the original dot.

vsWM as the retention of task-relevant visuospatial information through persistent neural activity. Furthermore, I presume that the loci of retention of this information are IPS (Todd and Marois, 2004, Xu and Chun, 2006) and also FEF (Courtney et al., 1998).

Engle and colleagues have summarized their theory of WM in the equality

WM = STM + top-down attention.

In addition, I suggest the following three equalities:

STM = FEF & IPS
top-down attention = dlPFC
WM = FEF & IPS with dlPFC

These equalities underlie much of my thinking about the neural basis of vsWM in this thesis. However, before I describe that, I will introduce the vsDR task.

I have restricted my studies to the vsDR task only. There are several reasons for this choice. First, the goal of the thesis is to study the neural basis of WM, and the simplicity of the vsDR task makes the mapping to neural activity more straightforward. For instance, unlike many other tasks such as the *n*-back task, the vsDR task most likely requires a narrower range of auxiliary mental processes such as updating of the contents in WM. Second, most of what is known about the cellular neurophysiology of WM comes from research on the vsDR task (Goldman-Rakic, 1995). Third, this is the task most studied by mechanistic models (Wang, 2001). Fourth, given the correlations between performance on the vsDR task and general intelligence (Kane et al., 2004, Kane et al., 2007), ADHD diagnosis (Westerberg et al., 2004), etc, the restriction to the study of one type of task only has a minor impact on the validity of the research in this thesis.

The basic vsDR (Figure 1) is the simplest possible WM task. It requires the brain to remember the location of a dot in visual space. At the beginning of the task, one or more cue stimuli flash onto the screen, simultaneously or sequentially. The subject has to remember their position during the following delay period. At response, the subject indicates where the stimuli had been presented. The specifics of the task

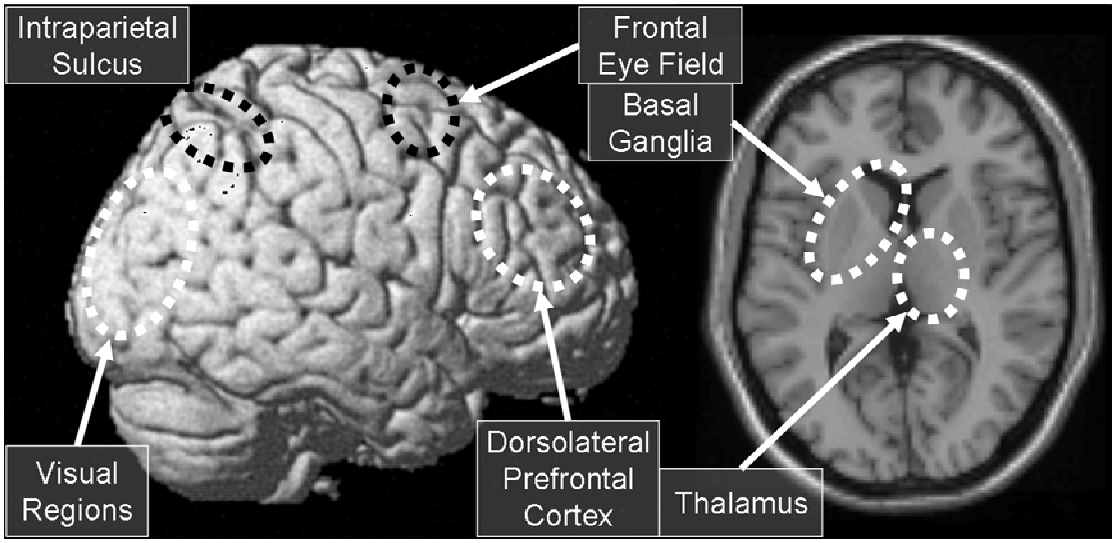

Figure 2. Approximate locations most of the regions activated commonly associated with vsWM. Left: neocortical regions. Right: subcortical regions (described in the *Discussion* section). Black regions are memory regions. White regions are auxiliary. The nomenclature follows Curtis (2006). Noted that the circled areas are functionally defined regions and do not match exactly the anatomical labels that some of them have.

may vary. For example, the stimuli do not have to be dots as in Figure 1, and the memory of the stimulus can be indicated by responding to a Yes/No question.

Performance on the vsDR task is commonly measured in three ways (see, e.g., Olesen et al., 2004). **Capacity** is the maximum number of memories a person can retain. **Accuracy** is the proportion of correct answers if the response can only be correct or incorrect. Otherwise the accuracy is the distance between cue and response. **Response time**, the time from the response request to the response, is not included inthis thesis, since it cannot be related to any of the neural mechanisms that we studied.

Despite the simplicity of the task, it is rich enough to probe many types of cognitive differences between individuals if various variations are added to the task. Through these variations, the difficulty level of different aspects of the task can be varied, and variations in the activity of the neural circuits determining task performance can be studied. The most common variations of the vsDR theme are

- Load variation (number of stimuli presented)
- Distracter presentation (presentation of irrelevant and disturbing stimuli)
- Dual tasks (simultaneous performance of another attention-demanding task)
- Lures (presentation of almost correct response alternatives)
- Regulation of the difficulty of chunking (the association of several stimuli)
- Sequential or simultaneous presentation of stimuli
- Temporal variation (e.g. length of delay period)

In addition, subjects may use different strategies to improve performance. This is a factor that is hard to control in experiments.

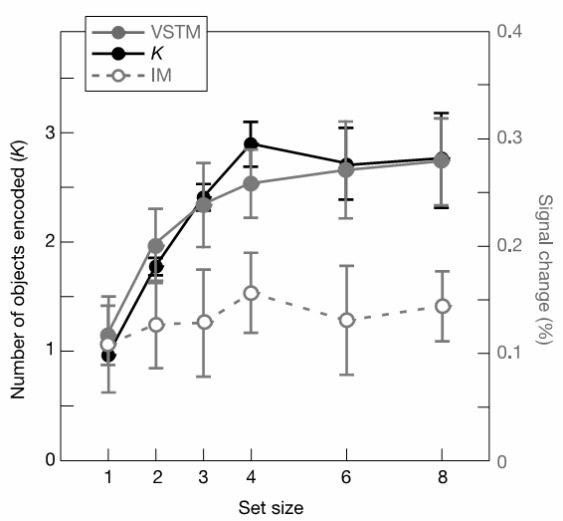

Figure 3. Brain activity in IPS tracks the number of remembered memories on a vsDR task (Todd and Marois, 2004). VSTM: IPS fMRI signal in the vsDR task. K: behavioral estimate of the number of stored memories. IM: IPS fMRI signal in an iconic memory task not thought to involve IPS. Figure taken from Todd and Marois (2004).

Of these task variations, distraction will be discussed in depth. Given the topic of this thesis, the best point of departure for this discussion will be the neural mechanisms involved in these variations. Therefore, I will now give an introduction to the neural basis of retention of information in vsWM.

Functional anatomy of vsWM

Our knowledge about the functional anatomy of vsWM comes mainly from two sources, neurophysiological recordings in monkeys and fMRI (D'Esposito, in press). Additional information has been provided from mechanistic modeling, EEG, positron emission tomography (PET) and lesion studies. Figure 2 shows the functional anatomy of the vsWM network. Visual stimuli enter V1[13] via the retina and thalamus. Then, early visual regions extract spatial information, which enters the memory regions in IPS and FEF, where it is stored. However, other regions are also important for the execution of the vsWM task. In particular, dlPFC has been implicated in important control functions, such as the focusing of attention on the task and the filtering of task-irrelevant information from memory. Below is a list of the brain regions investigated in this thesis and what is known about their role in vsWM. In the *Discussion* section, I describe other WM-related brain regions not included in the model and discuss the effects of their omission.

Visual regions

Spatial information is primarily processed in a chain of dorsal brain regions starting from V1 and including V2, V3 and V6 (Kandel et al., 2000), but also in ventral regions like V4 (Bartels and Zeki, 2000). These early visual regions are presumably of less importance for vsDR task performance, but capacity limitations here may be a

[13] The visual cortex is divided into a set of regions ordered in an enumerated list starting with V1. Generally, regions with lower numbers ("early regions") code for simple and concrete visual information, whereas regions with high numbers code for abstract visual information.

factor underlying one of the primary bottlenecks of human cognition, the attentional blink, which is the inability to encode information earlier than 500 ms after the processing of another stimulus (Marois and Ivanoff, 2005). The visual regions connect to IPS (Felleman and Van Essen, 1991), but also to area 8 (macaque FEF; Barbas, 1988).

Intraparietal Sulcus / area 7

Neurophysiological studies in macaques (Constantinidis and Steinmetz, 1996, Chafee and Goldman-Rakic, 1998, Chafee and Goldman-Rakic, 2000) and imaging studies in humans (Curtis et al., 2004, Todd and Marois, 2004, Xu and Chun, 2006) have revealed that IPS (Brodman area 7a/7ip in macaques) activates during all phases of a vsWM task. Activity in IPS (Todd and Marois, 2004), more specifically inferior IPS (Xu and Chun, 2006), reflects the number of stored memories in the basic vsDR task (Figure 3). Activity in the superior IPS, on the other hand, tracks the total complexity of objects held in memory (Xu and Chun, 2006).

Frontal Eye Field / Superior Frontal Sulcus / area 8

The frontal eye field (FEF) in humans lies partly in the posterior SFS, in area 6 (Paus, 1996, Kastner et al., 2007), and in the macaque in Brodmann area 8. FEF is a functionally defined area, SFS is a brain sulcus and Brodmann areas are defined based on histological characteristics. Together with IPS, FEF is the brain region most consistently activated during the vsDR task (Curtis, 2006). FEF and IPS are connected through monosynaptic connections (Andersen et al., 1990), and together the two regions constitute the fronto-parietal vsWM network (Chafee and Goldman-Rakic, 1998). The difference between memory activity in IPS and FEF is still not known, but the two regions might store different aspects of the stimuli. To solve the basic vsDR task, one can either use a retrospective code where the memory is stored, or a prospective code, where the planned answer is stored. A study by Curtis et al. (2004) suggests that activity in FEF encodes the upcoming response, whereas activity in IPS encodes the original memory.

Dorsolateral prefrontal cortex / Middle Frontal Gyrus / area 46

dlPFC consists of Brodmann areas 8, 9, 10 and 46 (Curtis and D'Esposito, 2003), but in this thesis I will use the terminology of Miller (Miller and Cohen, 2001) and use dlPFC to refer to its middle part, especially area 46, as opposed to FEF. Defined this way, dlPFC lies approximately in the middle part of the human middle frontal gyrus and macaque principal gyrus. dlPFC has been implicated in a wide range of higher cognitive functions including top-down attention, the inhibition of a prepotent response and general intelligence (Duncan and Owen, 2000, Duncan et al., 2000).

dlPFC has a large amount of connections to other associative brain regions (Felleman and Van Essen, 1991, Barbas, 2000, Burman et al., 2006), and activity in dlPFC has been found to modulate activity in regions as early as the V1 and V2 (Kastner and Ungerleider, 2000, Gazzaley et al., 2007). Newer fMRI and neurophysiological studies in humans indicate that dlPFC exerts its functions by maintaining action plans for the regulation of cortical processing in other regions via top-down bias signals (Desimone and Duncan, 1995, Miller and Cohen, 2001, Curtis and D'Esposito, 2003, Passingham and Sakai, 2004, Koechlin and Summerfield, 2007). Whether all the cognitive functions with which dlPFC is implicated fit into this framework is an open question. The types of operations performed by neurons in dlPFC are still unknown.

A cascade of cognitive control[14] that proceeds from anterior to posterior regions of the frontal lobe has recently been described (Fuster, 2001, Koechlin et al., 2003, Koechlin and Summerfield, 2007). Posterior regions control motor action, intermediate regions perform contextual control that influence posterior regions (sensory-motor coupling within a context), and anterior regions modify theintermediate regions based on past events, such as task sets. In this cascade, dlPFC lies toward the anterior end.

It is unclear exactly how to relate human and monkey data (Passingham and Sakai, 2004). The monkey data shows single neuron activity tuned to the position of the cue (Funahashi et al., 1989). On the other hand, a recent study (Kastner et al., 2007) found no such retinotopy[15] in the equivalent brain region in humans. Kastner et al. (2007) concluded that the two areas are not homologous. However, the task used by Kastner was relatively simple and might not activate dlPFC, which activates more when vsWM load increases (Olesen et al., 2004). Another possibility might be that earlier neurophysiological studies found retinotopy in the posterior part of macaque area 46 that lie adjacent to or inside the macaque FEF, and that activity in that region corresponds more to human FEF activity (Passingham and Sakai, 2004). The authors alternatively suggested that the difficulty in finding memory activity in the human area 46 is because the proportion of active cells is too low to be found with fMRI.

WM on the cellular level

What we know about WM on the cellular level comes almost exclusively from neurophysiological recordings[16] and investigations of neuroanatomy and cell morphology in monkeys (Goldman-Rakic, 1995, Fuster, 2001, Miller and Cohen, 2001, Constantinidis and Procyk, 2004, Constantinidis and Wang, 2004, Douglas and Martin, 2004, Passingham and Sakai, 2004, Compte, 2006, Funahashi, 2006). Fuster (1971) was the first to find cells with persistent activity related to memory in the brain. This activity had four important properties (Fuster, 2001): (1) It was absent after the action for which memory was required had been performed. (2) It was absent in the mere expectation of reward. (3) It was correlated with task performance. (4) It could be diminished or extinguished by distracting stimuli that cause poorer performance.

After the seminal discovery of persistent activity in the frontal cortex, such activity has been found in all the brain regions that have later been implicated in WM with fMRI, including FEF and IPS (Chafee and Goldman-Rakic, 1998), the inferotemporal cortex (Miller et al., 1996), the cingulate cortex (Niki and Watanabe, 1976), the mediodorsal nucleus of the thalamus (Fuster and Alexander, 1973), the basal ganglia (Hikosaka and Wurtz, 1983), as well as in a range of other areas not commonly implicated in vsWM (Constantinidis and Wang, 2004).

In the 1980s, Goldman-Rakic and colleagues (Funahashi et al., 1989, Goldman-Rakic, 1995) developed the oculomotor delayed response task, which is a version of the vsDR task with a load of 1 stimulus that requires subjects to fixate their gaze at a cross in the middle of the stimulus presentation screen while performing the task (Figure 4). By requiring the monkeys performing the task to keep their eyes still,

[14] Cognitive control is not clearly defined, but is often equated to "executive attention" (Miller and Cohen, 2001).
[15] Each cell in a visual region (including FEF and IPS) has a receptive field, a part of the visual field in which it codes for stimuli. Retinotopy is the orderly progression of receptive fields along the cortical surface, such that adjacent cells have adjacent receptive fields.
[16] The recording of the electrical activity of a nerve cell obtained by placing an electrode near the cell.

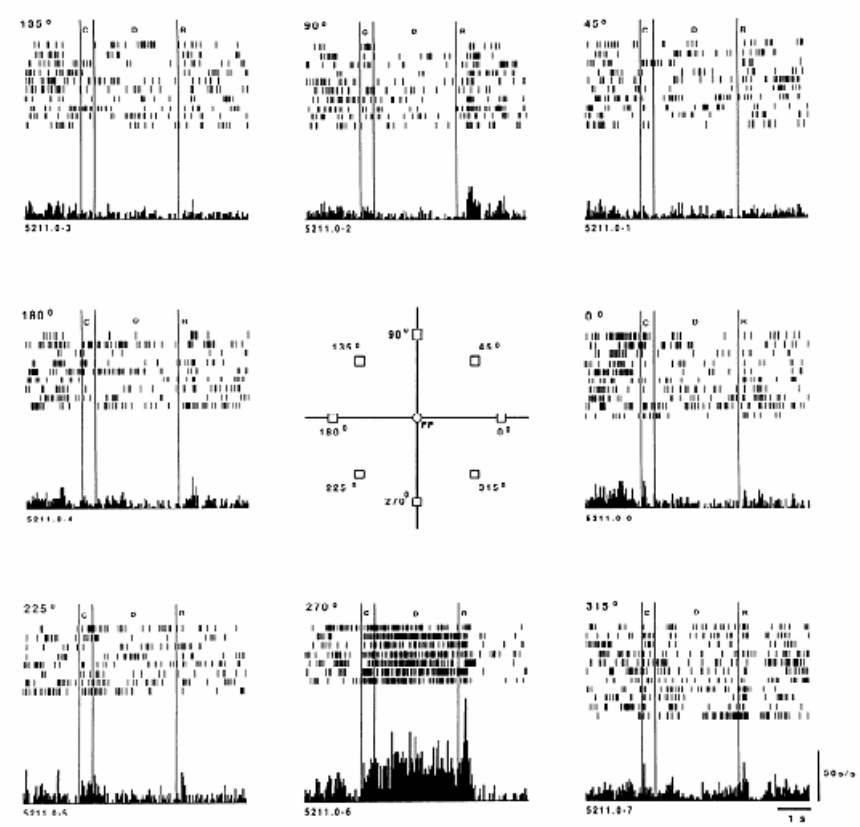

Figure 4. Recordings from a cell in the principal sulcus of a monkey performing the oculomotor delayed response task (Funahashi et al., 1989). Stimuli were presented on a screen at eight angles. Neural activity corresponding to stimuli of each direction is shown in the histograms. Above the histograms, action potentials from each trial are shown. Onsets of the cue, delay and response phases are indicated with vertical lines. This cell had a preferred direction of 270°. Figure taken from Funahashi et al. (1989).

it was possible to obtain neurophysiological recordings showing retinotopic coding of memories. The authors suggested that memories were coded through cells in dlPFC that selectively activate after stimulus presentation at a certain visual angle. Although newer theories dispute that memories are stored in dlPFC (see the *Dorsolateral prefrontal cortex / Middle Frontal Gyrus / area 46* section above), researchers generally consider the memory of spatial locations to be stored in the retinotopic maps.

Later, other researchers (Quintana and Fuster, 1999, Takeda and Funahashi, 2002) found two types of cells in frontal cortex, one type of cell with plateau or slowly receding activity coding for the stimulus and one type with ramping activity coding for the response. This firing behavior was found in both frontal and parietal cortices (Figure 5). Funahashi (1989) also described different temporal patterns of activity by describing cells as cue (C), delay (D) or response (R) selective, or a combination thereof.

There seems to be a discrepancy between human imaging data and monkey neurophysiology regarding distractibility. Monkey neurophysiology data indicates that activity in the posterior memory regions is not resistant to distraction, i.e., it is possible to diminish or abolish activity in parietal or temporal regions without causing poorer performance (Constantinidis and Steinmetz, 1996, Miller et al., 1996). This would disqualify IPS from being the store of spatial memories.

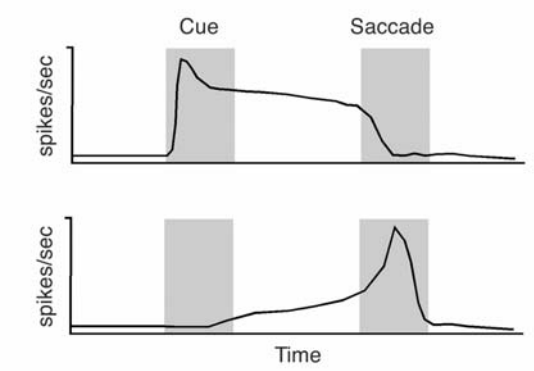

Figure 5. There are two types of firing patterns during the vsWM task in the monkey. One type of neuron decreases its activity and one type increases its activity (Fuster, 2001). Figure taken from Constantinidis and Procyk (2004).

A mechanistic model of persistent activity in vsWM

The neurophysiological explorations of the neuronal basis of vsWM-related persistent activity have made possible the development of mechanistic models of vsWM. With a mechanistic model, it is possible to evaluate the mechanisms behind the relationship between brain structure and brain activity or task performance[17]. The prevailing mechanistic model of vsWM delay phase activity is a network model of the Hopfield type. The model was originally developed to investigate mechanisms behind maintenance-related activity recorded from monkeys performing the oculomotor delayed response task (Camperi and Wang, 1998, Compte et al., 2000). It has been developed in this thesis and also by Macoveanu et al. (2006, 2007) to be able to relate structural factors to behavioral and brain activity data from humans performing vsDR tasks. Thus, it now encompasses several brain regions, and it is possible to store several memories in the model. This makes it possible for the first time to test mechanistic hypotheses for how factors such as myelination (Olesen et al., 2003) could affect vsWM capacity and other measures of task performance.

The structure of the model is described in the *Methods* section of the articles as well as in the *Methods* section of this thesis, and only described briefly here. For further introduction to the vsWM model as well as models for other types of WM, several review articles have been published (Wang, 2001, Brody et al., 2003, Brunel, 2003, Compte, 2006). See also Table 5 in the *Discussion* section. For an introduction to neural modeling in general, I refer to the text book by Dayan and Abbott (2001) and for an introduction to neurophysiology, I refer to Kandel et al. (2000). The model consists of one or several local cortical circuits in which memories are stored. Each local circuit represents one brain region (FEF, IPS or dlPFC) and is compared to one activation cluster (fMRI) or one electrode (EEG) when comparisons are made with experimental data. Each local circuit is a network of pyramidal cells and inhibitory interneurons[18] connected in an all-to-all fashion (Figure 6A). The pyramidal cells

[17] As contrasted with a statistical model. Somewhat simplified, a statistical model investigates the presence of a relationship, a mechanistic model the mechanisms behind it. See also the *Methods* section.
[18] Each brain region consists of a large set of local neural circuits. Each circuit consists of excitatory pyramidal cells and inhibitory interneurons that are connected (other cell types also exist). Activity in an excitatory (inhibitory) cell causes increased (decreased) activity in the cells to which it is connected.

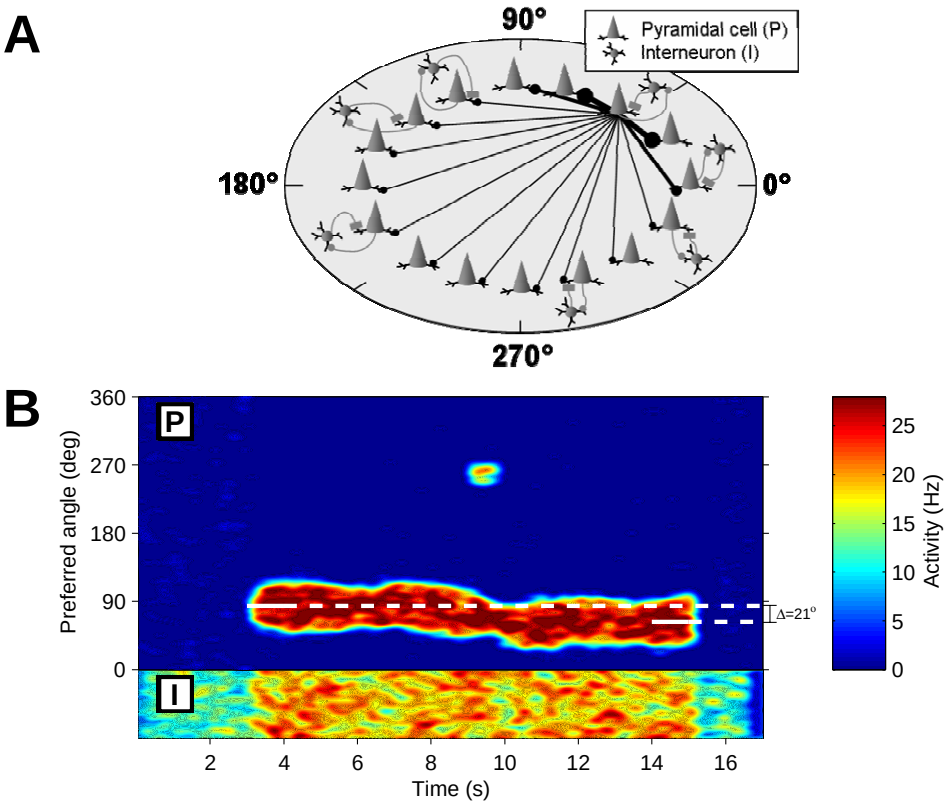

Figure 6. The vsWM model and underlying neurophysiological data. **(A)** Network architecture. The model consists of pyramidal cells and inhibitory interneurons. All neurons in the model are connected to each other. The pyramidal cells code for an angle in visual space, with neighboring pyramidal cells having effectively excitatory connections, whereas inhibitory connections dominate between distant cells. Figure taken from study V. **(B)** Example simulation. P: pyramidal cells. I: inhibitory interneurons. Pyramidal cells are aligned along the *y* axis according to their stimulus specificity. The network has two stable states, a memory and a no-memory state. After a stimulus is presented (t = 3 s in Figure 6B), a memory bump consisting of cells with higher activity stores the location of the stimulus. At the end of the task (t = 15 s), the location of the memory activity has shifted slightly, leading to a memory inaccuracy of 21°. This shift was largely brought about by a distracting stimulus presented at 265° at t = 9 s.

code for an angle in visual space. Pyramidal cells that encode similar angles have strong excitatory connections, whereas pyramidal cells coding for dissimilar stimuli have net inhibitory connections due to connections via inhibitory interneurons. Figure 6B shows a simulation of the task in a network with a capacity of 1 memory. Several important aspects of model behavior can be read out from the figure. The activity of cells in the memory bump is caused by excitatory connections among themselves that are strong enough to sustain increased firing despite the high inhibitory activity. Also, one can see that distant cells have net inhibitory connections, since the activity of cells not coding for the stimulus decreases. Inhibition of cells outside the bump is also the factor causing activity not to spread to the rest of the network. It is also possible to see that the net inhibition results from connections to inhibitory cells, since they

increase their activity during the memory period. Distracters are modeled as ordinary stimuli.

The model contains several of the basic ingredients that allow comparison with experimentally obtained brain activity and behavioral performance data from subjects performing the vsDR task:

- **Capacity limit:** Different memories tend to destabilize each other (Compte et al., 2000, Macoveanu et al., 2006), as exemplified by the distracter in Figure 6A, thereby limiting how many memories can be stored. The parameter values determining the exact capacity limit are still unknown, but it is possible to test the effect of parameter variations on capacity. In study V, we give a simple mathematical description of factors setting the capacity.
- **Comparability with experimentally obtained brain activity:** The model consists of individual cells with biophysically detailed synaptic dynamics, and in the model version used in studies I and II, the pyramidal input-output curves and morphology are relatively detailed. Recent versions of the model also contain several brain regions and a model of the hemodynamic response. This makes it possible to simulate EEG, fMRI and single cell recordings. Many of the early developments in the model were done to make model behavior similar to monkey experimental data. For instance, one early problem was to achieve physiologically realistic firing rates in both the memory and no-memory states.
- **Accuracy and memory decay:** Due to high variability in the input to model pyramidal cells, memory activity drifts over time (Compte et al., 2000). These random fluctuations can also cause transitions to the no-memory state (Wang, 1999, Compte et al., 2000, Tegnér et al., 2002). Both mechanisms lead to memory inaccuracy that increases progressively over time. Like the capacity limit, these factors can be measured in experiments.

The model has the very important advantage in comparison with models that are not biologically based, e.g. ACT-R (Anderson et al., 1996, Anderson et al., 2004), that there is the possibility for connection to neuroanatomical and molecular data. By being biologically based, it is possible to test the effect of structural, neuromodulatory and other biophysical changes on activity and behavior. Through a tour de force effort, Brunel and others (Amit and Brunel, 1997, Brunel, 2000, Renart et al., 2003) created a relatively simple set of equations that are possible to mathematically analyze in order to understand the relationship between model parameters and the presence or absence of stable mnemonic activity. This has providing a precise and intuitive understanding of many of the factors governing model behavior.

Mechanisms determining task performance – Modeling

To understand how to map behavioral performance to neural mechanisms, we need to study performance in the mechanistic model. Model performance can be measured as stability/capacity, drift and the effect of distracters on these. These can be mapped to the behavioral measures of capacity, accuracy in a task with a yes/no response and accuracy in a task where performance is measured as the distance between cue and response locations, and also to memory decay. Several neuronal mechanisms can influence the same behavioral measure. For instance, poor accuracy can be the result both of strong drift of and of loss of memory activity. Therefore, it may be difficult to draw conclusions regarding neural mechanisms from experimental studies where conventional measures of performance are used.

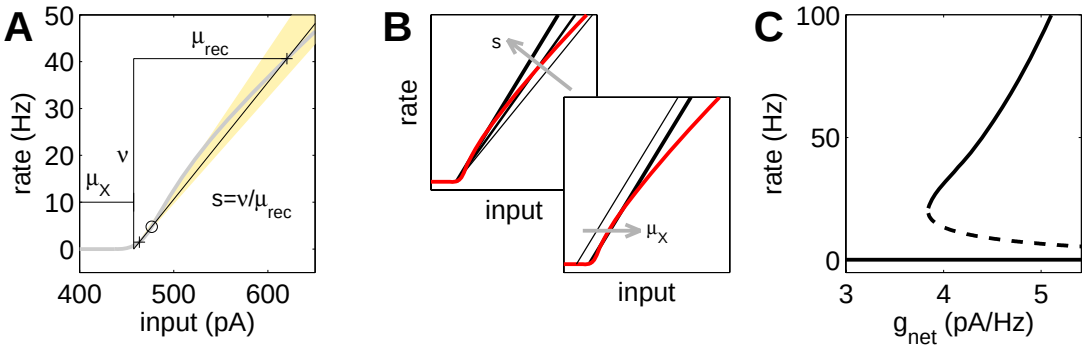

Figure 7. The graphical analysis by Brunel (2000). **(A)** Neuronal input-output curve describing mean output activity as a function of the mean synaptic current (pA) input it receives from other neurons (grey). The current can be divided into current arriving from outside the network (μ_X) and current arriving via recurrent network connections (μ_{rec}). The diagonal line is the current entering the network as a function of the network firing rate (ν). The slope of this line, *s*, is the synaptic connection strength. Intersections are stable states (fixed points) in the network. Upper +: memory fixed point. Lower +: no-memory fixed point. ○: activation threshold fixed point. Golden region: area where the grey curve and the black line intersect. **(B)** Decreasing (increasing) effective synaptic connection strength increases the slope *s* and leads to lower (higher) memory activity. Increasing (decreasing) the external input (μ_X) leads to increased (decreased) memory activity. **(C)** The mean activity of the memory state (upper solid line), the activation threshold (dashed line) and the no-memory state (lower solids line) as a function of the effective connection strength, $g_{net} = 1/s$. Figure adapted from study V.

Unfortunately, no rigorous network analysis has been performed to quantify the relationship between activity and stability yet. However, in a graphical analysis of his network equations, Brunel (2000) presented a function for how the mean activity level of memory activity co-increases with synaptic connection strength. In study V, I further developed this model to incorporate multiple memories so that the model can be used to study vsWM capacity. Figure 7 shows a modified and simplified version of the graphical network analysis. Basically, the activity of a neuron in the network depends on the amount of current (excitatory input) it receives (grey curve in Figure 7A). This input comes partly from outside the network, but since the neuron is strongly connected to itself and its neighboring neurons, each action potential results in a certain amount of input that is fed back into the neuron itself. The black line is the input as a function of activity. When the line is positioned as in Figure 7A, a firing rate of 20 Hz leads to an input of 540 pA (flip Figure 7A 90° to view input as a function of rate). The slope *s* of the line (after having flipped Figure 7A back again) is related to the effective synaptic connection strength in the network (approximately the inverse of the excitatory – inhibitory connection strength). If the connection strength is weak, *s* is high (Figure 7B). Increasing the rate in the network does not result in much more input into the cell. If the connection strength is high, *s* is small.

In the absence of a stimulus, memory activity is stable only when it can sustain itself. This happens when the curve and line intersect, which is when the current caused by network activity (black line) causes activity (grey line) that leads to the exact same amount of current, i.e., the activity can reproduce/sustain itself. This

means that memories only exist in the narrow range of values of *s* in which the line and curve intersect (golden region in Figure 7A). Figure 7B shows that by varying *s* (upper panel) or μ_X (lower panel), it is possible to regulate memory activity. Figure 7C shows the stable mnemonic activity as a function of the effective synaptic connection strength, g_{net}. Two important things can be read out from the figure. First, when the connection strength is too low, memories cannot exist. Second, note the dashed line. This line functions as an activation / deactivation threshold. Firing rates above the threshold will increase until they reach the stable mnemonic activity level. Rates below this threshold will decrease until they reach the no-memory state.

For what follows, it is important to note the simplification that has been done in this analysis. Every memory bump consists of several cells (see Figure 6B). Yet, the graphical analysis only describes a single cell. This is because the graphical analysis requires the simplification assumption that all cells in the bump have the same rate.

Having introduced Brunel's graphical analysis, we are now ready to discuss stability, drift and the effect of distracters.

Memory stability and the effect of distraction

Every cell in the network receives a time-varying and random bombardment of action potentials as input. Therefore, activity in the memory bump fluctuates around the mean values shown in Figure 7C. If these fluctuations bring the network below the activation threshold, the memory will be lost. Somewhat simplified, stability is therefore the distance between the memory state and the activation threshold in Brunel's model.

This means that higher memory stability can be obtained either by increasing the distance to the activation threshold, for instance by increasing excitatory connections, or by reducing current fluctuations. Slow synapses like the NMDA synapse will spread the input current evenly across a relatively long segment of time (around 150 ms), which reduces fluctuations (Wang, 1999, Tegnér et al., 2002, Compte, 2006). The random fluctuations are also a mechanism for memory decay. For example, if there is a constant chance at each time point of losing the memory state due to fluctuations, then the model would produce an exponential curve of forgetting.

Distracters can also cause the memory network to forget (Compte et al., 2000, Wang et al., 2004). Since cells in the mechanistic model that code for different memories have an effectively inhibitory connectivity, it is clear that this should be true for distracters too, since they can also be considered to be distant memories. The presentation of a distracter therefore leads to a large fluctuation of the inhibitory input entering the bump cells. Compte et al. (2000) investigated distractibility with a model network having a capacity of 1 memory. He found that there is a competition between the distracter and the memory to the effect that the one with the highest activity remains in the memory buffer whereas the activity of the other dies out. In this way, distraction leads to instability. However, even when memory capacity is above 1 memory, the retention of an extra stimulus should destabilize the network: the distracter activity leads to increased negative current in the network, bringing activity closer to the activation threshold.

Drift and distracter-induced shifts in memory locations

As shown in Figure 6B, the position of memory bump moves erratically back and forth throughout the delay period. The mechanisms behind this drift are best

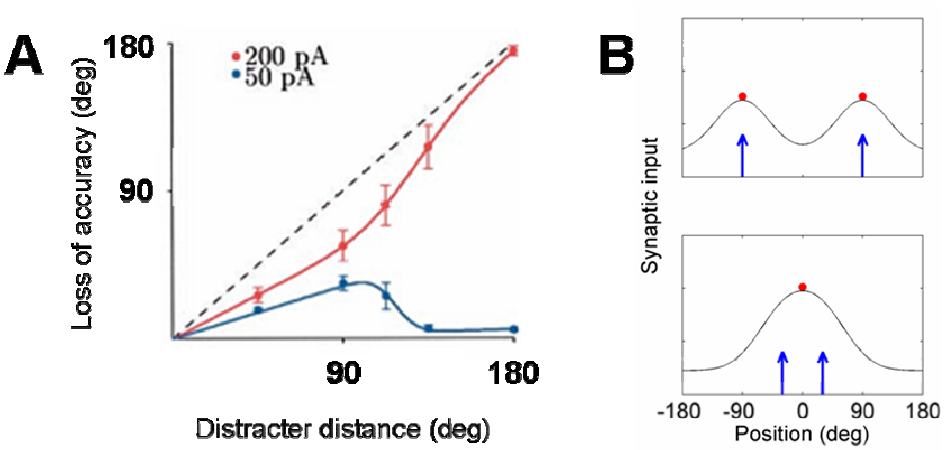

Figure 8. The effect of a distracter on memory activity as a function of distance in a network with the capacity to hold 1 memory. **(A)** If the distracter stimulus is presented far away from the stimulus and is strong, the location of memory activity moves to the position of the distracter (red curve). When the stimulus is weak (blue curve), the memory instead survives. If the distracter is presented close to the stimulus, memory activity moves to a position in between the distracter and the original memory activity. Adapted from Compte et al. (2000). **(B)** A mechanism for the distance-dependent distracter effect. Blue arrows: position of memory and distracter activity. Black curve: synaptic input into cells coding for different angles. Red dots: position of cell with maximum input. After the presentation of a distracter, memory activity moves to the cells with the highest synaptic input. If the two are far away from each other (upper panel), there is one maximum at the distracter position and one at the memory. When the two are close to each other (lower panel), cells that are between the two receive the highest amount of input.

explained by studying distracters. I therefore first explain how distracters cause memory inaccuracy (as opposed to instability, which has been explained above), and then explain drift. Compte et al. (2000) found that distracters affected memory activity differently depending on their distance from the memory (Figure 8A, 8B). Distracters presented at a large distance from the memory tended to either destabilize memory activity or be destabilized itself, as explained in the previous subsection. On the other hand, distracters presented close to the memory bump did not destabilize activity. Instead, they introduced a shift in the position of the memory, so that after distraction, the position of the memory was the mean of the original position of the memory and the position of the distracter. When a distracter is presented close to the memory, cells located between the cells coding for the distracter and the memory will receive excitation from both groups of cells (Figure 8B), causing them to have the highest activity of all cells in the network. After distraction, the new location of memory activity will be a weighted average of the old memory and distracter cells. Hence, if memory activity is high, it is harder to dislocate and accuracy will be higher.

To understand drift, one can think of an action potential in a cell close to the memory as a very small distracter. Each action potential results in a small shift of the bump. Likewise, since each cell also receives random synaptic input from the rest of the brain, this external input also shifts the position of the bump. This means that the low surrounding activity and the random input from the rest of the brain affects

accuracy in the same way as distracters (Camperi and Wang, 1998, Compte et al., 2000), but to a much lesser extent, since the activity they cause outside the memory bump is much lower than that caused by a distracter. Like memory instability, drift is caused by current fluctuations. Therefore, increased activity and slower time constants will lead to less drift.

Before describing the methods used in this thesis, I will just say a few words about development and training of vsWM, which were the focus of studies I and IV.

Development and training of vsWM

There is an improvement in WM capacity and associated cognitive functions during childhood and adolescence until the age of about 18 years. WM capacity improves with as much as 2 – 3 memories (Fry and Hale, 2000, Gathercole et al., 2004). The ability to ignore interference also improves (Hale et al., 1997, Ridderinkhof et al., 1997, Kramer et al., 2005). Performance of vsWM tasks seems to activate the same areas in both children and adults (Klingberg et al., 2002). During development, vsWM-related brain activity increases in FEF and IPS (Klingberg et al., 2002, Olesen et al., 2003), although previous studies have not investigate whether this is due to encoding-, retention- or response-related activity. In addition, fractional anisotropy, a measure of myelination, suggests that myelination also increases in the fronto-parietal white matter connecting FEF and IPS (Olesen et al., 2003). Anatomical studies show that cortical development takes place sequentially, with peripheral regions (such as V1 and M1) maturing earlier and regions related to higher cognitive functions later (Huttenlocher and Dabholkar, 1997). Some of the latest regions to mature are the associative cortical regions in the vsWM network. This indicates that it should be possible to conduct developmental studies that include cognitive tasks designed to target the functions of each specific region.

It has been shown in several studies that it is also possible to train vsWM (Olesen et al., 2004, Klingberg et al., 2005, Westerberg et al., 2007, Westerberg and Klingberg, 2007). Olesen et al. (2004) showed that training primarily causes changes in dlPFC and IPS, but also in superior parietal cortex and subcortical regions. Thus, the mechanisms underlying training could differ from those underlying development. It could be that development induces changes in the fronto-parietal retention network, whereas training induces changes mostly in dlPFC.

Methods

This section gives a brief general introduction to the research methods used, emphasizing the advantages and disadvantages of the methods when applying them to WM research, as well as how to connect them to the computational model. Lengthier descriptions can be found in the studies and in the references given below.

Mechanistic and statistical mathematical modeling

In this thesis, two types of mathematical models were used to analyze experimentally obtained brain activity and behavior, a mechanistic model (described in the *Introduction* section) and statistical models (described below). Despite being different, they also have commonalities. Since they are both mathematical models, they both answer quantitative questions about a system. For example, a statistical model class called generalized linear model is used to model fMRI data to test whether brain regions aresignificantly more active during memory retention than during a condition not requiring memory.

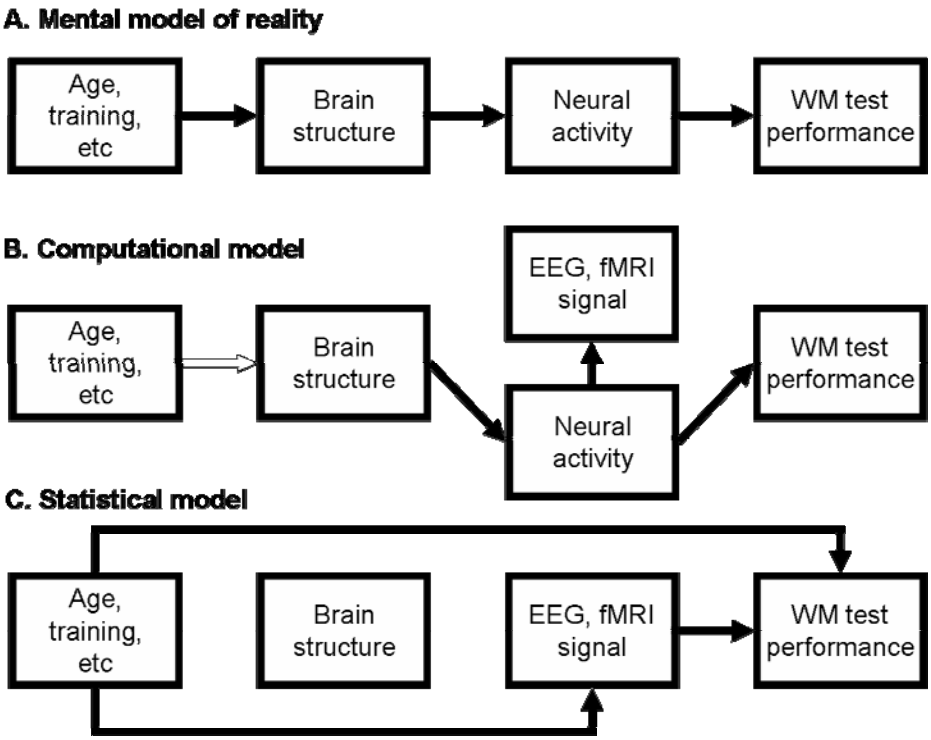

Figure 9. Relationship between age or training, vsWM network structure, neural activity, EEG/fMRI signal and behavioral performance. **(A)** In my mental model of reality, brain structure changes as a result of age, WM training and other variables. Changes in brain structure in turn lead to changes in brain activity, which leads to differences in WM test performance, as shown by the black arrows. **(B)** The mechanistic model models the effect of structural parameters on brain activity, the stability of which leads to WM test performance. In addition, the link between neural activity and EEG/fMRI signal is modeled. Age and training are not explicitly modeled. Instead, their effect on brain structure is based on hypotheses from previous research (white arrow). **(C)** The statistical data modeling in this thesis was used to find non-mechanistic links between age and training, EEG/fMRI signal and WM test performance.

The features of a system that are needed to answer the question are included in the model and the effect of these features (but only these features) on system behavior can be tested. This means that the questions that can be answered are defined by the features included in the model. The statistical models in this thesis incorporated variability, but not much more, whereas the mechanistic models incorporated mechanisms relating brain structure to activity and performance, but did not incorporate variability. Because of this difference, the two model types answer different questions. The statistical model answers the question whether the observed data could have been due purely to randomness, whereas the mechanistic model includes mechanisms, e.g. between WM network structure and WM activity. Thus, it can be used to test whether the mechanisms included in the model can explain the data. In study III, we tested the effects of measurement inaccuracy on estimates of connection strength based on the analysis of an autoregressive model. That model lies somewhere in between the other two models. It models connections between brain

regions, but not the nonlinearities that we believe are important in explaining persistent activity. In addition, it models variability.

Necessary or just sufficient?

To infer that a mechanism causes observed data, all other mechanisms (or the plausible ones) need to be ruled out. Given that all plausible mechanisms must be excluded in order to infer a mechanism, this is very difficult. Still, this was the aim of both study I and II. Study III was purely technical and study IV did not investigate any mechanism. The aim of study V was to find a sufficient mechanism.

The use of models in this thesis

The aim of the thesis was to find a relationship between brain structure, neural activity and task performance, and then investigate how that relationship was affected by factors such as age or training. My mental model of this relationship is described by the flowchart in Figure 9A. With mechanistic modeling, a link from brain structure to brain activity and from brain activity to WM tasks performance can be established (Figure 9B). Below, it is shown how this link is made. However, since current mechanistic models are not equipped to model sources of variation arising from inter-individual variability, unmodeled brain activity, etc., we used statistical models (Figure 9C) to exclude the possibility that unmodeled variability (noise) caused the observed relationships. On the other hand, the experimental tools used to measure brain activity, fMRI and EEG, do not measure neural activity as described so far in this thesis, but only indirect measures of neural activity[19]. To draw conclusions about the relationship between brain structure and task performance, we must therefore incorporate a model of the link between neural activity and fMRI/EEG signals in the computational model (see below).

Since mechanistic models incorporate mechanisms and statistical models model noise, the two types of mathematical model are complementary. Combined, they can be used to find links from group or individual characteristics to brain activity and behavioral data. The statistical models are described under the *Functional magnetic resonance imaging* and *EEG* sections below, and the mechanistic models are discussed in the *A mechanistic model of persistent activity in vsWM*, *Mechanisms determining task performance – Modeling* and *Hemodynamic model* sections.

There are several ways in which a mechanism can be falsified. This would occur if the model cannot explain experimentally obtained a) EEG/fMRI signals, b) measured task performance, or c) the relationship between EEG/fMRI signals and WM test performance.

vsWM tasks and participants

Although the tasks in the studies differed slightly (Table 2), subjects always had to remember the location of the stimuli and respond by clicking with a computer mouse. One reason for differences between the tasks is that the experiments had all been used in other studies in addition to those included in this thesis (Olesen et al., 2007, McNab and Klingberg, in press, Persson et al., submitted). For example, the sequence used in studies II and IV is a standard test sequence used in all studies of WM training in the Developmental Cognitive Neuroscience group.

[19] Note that an EEG/fMRI signal is often simply referred to as "activity", unless the author wants to explicitly distinguish it from neural firing rate.

In study II, the computational model was compared to a vsDR task with dots arranged in a 4-by-4 grid. Task differences such as this are presumably of minor importance, but their effects were not investigated. The most important difference between the tasks is presumably the load. At high loads, dlPFC activates (Curtis and D'Esposito, 2003). The type of subjects tested presumably also had an effect on the conclusions, since the FEF – SFS network, and in particular dlPFC, are less developed in children than in adults (Huttenlocher and Dabholkar, 1997). The data used in study II and IV were from children with epilepsy (of widely varying etiology) before and after training, but these effects were not investigated in study II. Since there was no common etiology in the participants, it is unlikely that the structure of the brains of the children differed in any systematic way. Thus, epilepsy presumably had a small effect on the results in study II.

Functional magnetic resonance imaging

The fMRI signal refers to a blood-oxygenation level dependent (BOLD) signal caused by brain activity and measured in a magnetic resonance scanner (Ogawa et al., 1990). Images can be constructed from this data and aligned to images of brain structure and give an accurate localization of this signal (Friston et al., 1995). In this way, brain activity can be measured indirectly by measuring the BOLD signal, which is induced inflow of oxygenated cerebral blood to a brain region (Attwell and Iadecola, 2002). The technique – functional magnetic resonance imaging (fMRI) – is perhaps the most common research tool for measuring brain activity in the field of cognitive neuroscience (Gazzaniga et al., 2002). The standard procedure for fMRI data analysis is the statistical parametric mapping method, described in Frackowiak et al. (2004), and the specifics are found in studies I and V. Here, I discuss aspects related to the mechanistic model that was combined with the fMRI data.

The magnetic resonance scanner provides data with high spatial and temporal resolution, but blood flow induced even by transient and localized neural activity is sluggish, which is the major drawback with the technique (Frackowiak et al., 2004). The duration of the hemodynamic response is of the order of 10-15 s (Frackowiak et al., 2004). However, by optimizing the statistical data processing, a higher temporal resolution of up to several hundreds of milliseconds can be obtained.

The relationship between the BOLD signal and underlying brain activity is unclear (Attwell and Iadecola, 2002). The debate has been intense and two main problems have been discussed. First, the extent to which the BOLD signal reflects neural activity (action potentials) or synaptic currents has been debated. Synaptic signaling with glutamate and $GABA_A$ leads to a release of post-synaptic nitric oxide, which causes blood vessels to dilate (Attwell and Iadecola, 2002). Since the amount of nitric oxide that is produced by the post-synaptic cell is proportional to its input,

Table 2. Differences in subjects and tasks between the studies.

Study	Subjects	Layout of dots	Distr-action	vsWM load	vsWM training	Response	Performance measure
I	Children and adults	Equal radius	Yes	3	No	Click on one dot	Distance
II, IV	Epileptic children	4-by-4 grid	No	Capacity limit	Yes	Click on all dots	Correct/ Incorrect
V	Adults	Equal radius	Both	3/5	No	Yes/No	Correct/ Incorrect

and since the fMRI signal correlates slightly better with synaptic signaling than with neural spiking, it is thought that synaptic rather than spiking underlies the BOLD response (Logothetis et al., 2001, Attwell and Iadecola, 2002). However, the difference in correlation between synaptic and spiking activity and the BOLD signal is only small (Logothetis et al., 2001, Mukamel et al., 2005). Still, a common objection to the technique is that the BOLD signal in a brain region could mainly reflect input from other regions. Second, it is impossible to distinguish between the activity of excitatory and inhibitory cells with fMRI, although there is evidence that most of the signal reflects pyramidal cell activity (Attwell and Iadecola, 2002). Therefore, it is theoretically possible that external signaling to inhibitory cells could lead to simultaneously increased BOLD signal and decreased pyramidal cell overall activity (Almeida and Stetter, 2002). This issue could cause problems for connecting the mechanistic model to fMRI. Those problems are discussed in the *Hemodynamic model* section below.

Cognitive subtraction

Cognitive subtraction was used to isolate activity and task performance specifically related to vsWM. This implies using a control task that is very similar to the vsDR task but with no memory demands. Cognitive subtraction isolates memory activity by subtracting BOLD activity induced by the control task from activity induced by the vsDR task. Experimental data obtained through cognitive subtraction can also be readily compared to output from the mechanistic model, since the model only contains the aspects of activity that are related to vsWM.

Statistical analysis

To statistically analyze the fMRI data in this thesis, piecewise constant regressors were convolved with a linear model of the hemodynamic response, and a linear combination of regressors (a generalized linear model) was fitted to the BOLD signal, as is standard procedure (Frackowiak et al., 2004). Regressors for cognitive epochs (encoding, maintenance, response) as well as confounding factors, such as low- and high-frequency noise, were included. This type of study design, where one statistically separates brain activity from different task epochs, is called an event-related design. Tests for significance were performed on the model using analysis of variance (ANOVA).

Hemodynamic model

vsWM model activity must be translatable into BOLD signals to be able to relate it to fMRI. One is then confronted with two choices. The first choice regards the type of neural activity, synaptic or spiking activity, from which to calculate the BOLD response. Since there are instances when synaptic activity is anti-correlated with spiking activity, BOLD and spiking activity could also be anti-correlated (Almeida and Stetter, 2002). However, this confusing situation does not arise during vsWM maintenance, because it could only take place during situations of external driving of inhibitory cells, which does not occur during maintenance, where activity is self-sustained. Nor is it likely that the situation would arise because of external inputs from dlPFC (study V), since they are presumably net excitatory, and because the bias currents in that study were very small compared to recurrent currents. To test the effect of using spiking or synaptic activity to calculate the BOLD signal, we performed calculations with both signals in study I (Figure 10A). As expected, differences were small. In study V, we did not explicitly calculate the BOLD signal.

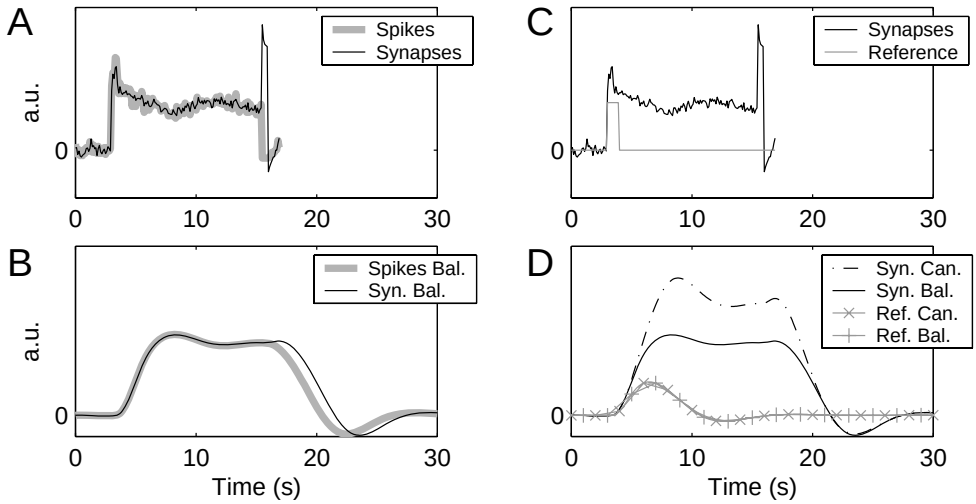

Figure 10. Simulating BOLD activity. **(A)** Synaptic (thin) or spiking (thick) neural activity were simulated, and found to be very similar. **(B)** BOLD activity is generated by feeding neural activity into a non-linear function (the SPM "balloon model"; Friston et al., 2000). **(C-D)** In most fMRI studies, the non-linear response is approximated by a linear function (the SPM "canonical hemodynamic function"; Friston et al., 1998). **(C)** Gray: synaptic activity. Black: a unit length, unit amplitude reference function. **(D)** The main effect of the non-linear ballon model is saturation of the BOLD response at high neural activity. a.u.: arbitrary units. Same data as in Figure 4, study I.

The second choice is the choice between a linear and a saturating, non-linear, hemodynamic model (Figure 10B; Friston et al., 2000). In linear models, twice the neural activity causes a BOLD signal which is twice as strong, whereas saturating models give rise to less than that. Although quantitatively different, the models behave in a qualitatively similar way. To conclude, the BOLD signal seems to give a qualitatively, albeit not necessarily quantitatively reliable measure of vsWM neural activity.

In keeping with Deco et al. (2004), a linear model was used in study I.

EEG

As in the *Functional magnetic resonance imaging* section, I mainly discuss issues concerning the combination of EEG measurements with the mechanistic model. I refer to textbooks (Nunez, 1995, Nunez and Srinivasan, 2005) for general information about the electroencephalogram (EEG) and to studies II and IV for specifics.

EEG is one of the oldest techniques for measuring neural activity (Berger, 1929). It essentially measures currents flowing in the trunks of the apical dendrite of cortical pyramidal cells by placing electrodes on the skull. Signal strength from subcortical regions is attenuated because of the distance to the electrode and can hardly be measured. The reason why pyramidal apical dendritical currents can be measured is because they are aligned, so that currents sum instead of cancel each other, as would be the case if they had different orientations.

Where fMRI has its advantage, EEG has its largest disadvantage. It has very poor spatial resolution. Spatial resolution can be improved by adding more electrodes and by deconvolving the signal using surface Laplacian deconvolution techniques (Babiloni et al., 1998). It is also possible to create an image of brain activity by solving the so-called "inverse problem", where EEG signals measured outside the skull are projected onto the cortex (Baillet et al., 2001). However, the solution is not unique, and may be of poor quality when electrodes are few. In the data analyzed for studies II and IV, the standard 10/20 system consisting of 19 electrodes was used. If there are very specific anatomical hypotheses, one can also try source reconstruction (Baillet et al., 2001). Here, one assumes that all brain activity of interest is located in one or a few positions (sources), and EEG activity is projected onto these sources. The poor resolution of EEG makes the connection to the mechanistic model more difficult. For example, it is difficult to separate EEG activity in FEF and dlPFC,.

The main advantage with EEG is the high temporal resolution and the relative ease of acquisition. High temporal resolution has many advantages. It is of course easier to clearly separate task delay and response. More important in this thesis is that it is possible to investigate the directionality of connections in the vsWM brain network. This is harder with fMRI. Finally, although the neurophysiology of the different EEG frequency bands is poorly understood, it is believed that low frequency bands reflect neural communication both between and within brain areas, especially including the thalamus (Nunez, 1995). Activity in higher frequency bands primarily reflects local communication within a brain region (Nunez, 1995).

EEG power, coherence and directed connectivity (directed transfer function, DTF) were analyzed with an ANOVA on a general linear model in the same way as the fMRI data, but without convolving regressors with the hemodynamic response. The use of a linear model may seem awkward considering that these measures are non-Gaussian whereas an ANOVA requires Gaussian errors. However, under many circumstances the central limit theorem applies and general linear models can be fitted to the data (Kiebel et al., 2005).

Biophysical modeling of EEG

In study II, we simulated local field potentials by calculating the potential difference between the soma and the distal apical dendrite of model pyramidal cells. The procedure is described in that study and here we only summarize the discussion regarding the feasibility of this approach.

There were two main difficulties with the biophysical simulation of EEG. The first was that in order to accurately simulate EEG, an accurate head model is needed, because the way that local field potentials mix to become EEG is determined by the geometry and conductivity of the brain, scalp and skull (Baillet et al., 2001, Kiebel et al., 2006). However, this problem seems to be smaller for measurements of effective connectivity with EEG (Babiloni et al., 2004).

The second and more serious problem is the complexity of the EEG signal, which makes it harder to simulate than the BOLD signal. In particular, since much of the low frequency activity is produced by interactions between cortex and thalamus (Nunez, 1995), a model that includes the thalamus should be used to analyze these effects. However, the neurophysiological knowledge needed to construct such a model does not exist, and standard models of EEG typically ignore the thalamus (Jansen and Rit, 1995, David et al., 2006, Grimbert and Faugeras, 2006). Higher frequencies are easier to simulate because of their primarily local origin.

Our model of the EEG signal is relatively accurate compared to several previous biophysical models with spiking cells, in which the EEG signal has been modeled as simulated synaptic activity (Compte et al., 2000, Tegnér et al., 2002).

The mean-field approximation

In study V, we found analytical solutions for the stable states in IPS memory network as well as ways in which these could be regulated by dlPFC signals. This was done by formulating a set of eight equations per brain region (Amit and Brunel, 1997), and then reducing these to a single equation (supplementary material of study V).

How can the synaptic currents in a network of thousands of cells be reduced to just eight? To formulate these equations, the so-called mean field approximation needs to be performed (Renart et al., 2003). This approximation is based on the following observation: any function, in this case the functions describing the statistical properties of the synaptic input into a cell, can be described in terms of moments of progressively higher order (mean, variance, skewness, kurtosis, and so on). Due to the central limit theorem, the contributions of the thousands of inputs that a cell receives should average out and all higher moments should be very small compared to the mean input, which means that they could be ignored and the synaptic input function replaced by its mean.

However, the brain is characterized by a delicate balance between excitatory and inhibitory inputs that almost cancel each other. Thus, the mean synaptic input is relatively small and the variance is no longer possible to neglect, although higher moments are. If one does a mean-field approximation of the synaptic inputs by replacing them with their mean and variance, then one arrives at the eight equations in study V. This powerful technique has been used by Amit, Brunel, Sompolinsky and Hertz, among others (Amit et al., 1985, Hertz, 1991, Amit and Brunel, 1997, Brunel, 2000), and several of its applications are described by Renart et al. (2003).

Summary of Studies I – V

Study I – Stronger synaptic connectivity as a mechanism behind development of working memory-related brain activity during childhood

vsWM during childhood (Fry and Hale, 2000, Gathercole et al., 2004). had been related to increased activity in FEF and IPS (Klingberg et al., 2002), but the neural mechanisms behind development had not been found, nor was it clear whether development was related specifically to encoding, maintenance or response selection.

Three neural changes occurring during childhood had been suggested to underlie vsWM development: synaptic pruning, synaptic strengthening and increased myelination, which increases axonal conduction speed (Yakovlev and Lecours, 1967, Huttenlocher, 1979, Lamantia and Rakic, 1990, Bourgeois et al., 2000). Based on previous studies (Olesen et al., 2003), myelination was a likely cause of vsWM development. We tested hypothetical developmental effects of these mechanisms (H1 – H5) by creating one child and one adult version of the IPS – FEF vsWM network for each hypothesis and performing network simulations (Figure 11). The hypotheses differed in mean simulated fMRI activity and inter-regional correlations. We then compared the simulation results with the delay-phase fMRI data extracted from FEF and IPS in children and adults. Differences in mean activity were tested with an event-related design. Fronto-parietal correlation coefficients were also calculated.

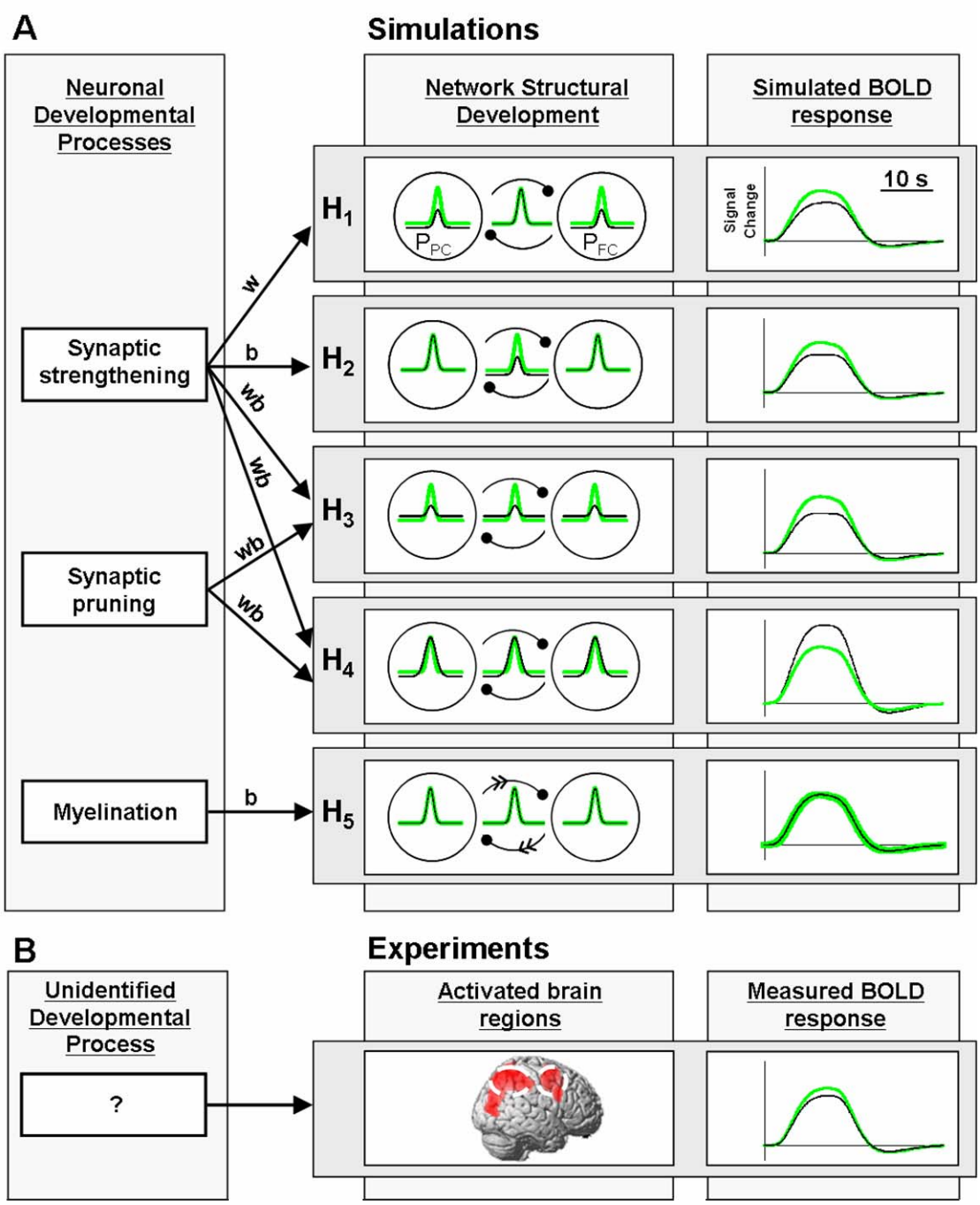

Figure 11. The logical structure of study 1. **(A) Simulations.** Column 1: neuronal developmental processes. Column 2: developmental hypotheses H1-H5. Black: 'child' network. Green: 'adult' network. The circles represent the parietal and frontal pyramidal cell populations, respectively. The strengths of connections within a region are indicated by the connection curves inside the circles. The connection curves show that cells coding for similar stimuli are strongly connected, whereas distant cells are weakly connected. The connection curves between the circles show the connection strength between regions. Column 3: BOLD signal predictions from the hypotheses. **(B) Experiments:** Column 2: whole-brain delay-phase activity. Column 3: fronto-parietal delay-phase BOLD signal (arbitrary units).

Stronger inter-regional synaptic connectivity predicted the fMRI results. In addition, a comparison of simulated distractibility in the model and in study participants showed that the model predicted behavioral differences too. We therefore concluded that stronger inter-regional synaptic connectivity caused development of vsWM.

To causally link structural changes to changes in brain activity and behavior via a certain mechanism, all other mechanisms must be falsified. This is very difficult, because it is possible that our results could have been caused by mechanisms that we did not evaluate. But even if our inference turns out not to be correct, the study still gave useful information about the mechanisms behind the development of vsWM. Before the study, myelination was found to be important for development. We could now refute the hypothesis that faster fronto-parietal neuronal signaling caused by increased myelination improves vsWM.

One drawback of the study was that mechanisms related to development in neuromodulatory systems such as dopamine could not be tested. Another factor that could have affected our results was that dlPFC activity was higher in adults than in children (see Olesen et al., 2007 for a whole-brain analysis of this fMRI data set), which was not found in Klingberg et al. (2002). This could have been due to the fact that distracters were included in the present task. Thus, dlPFC might be important for the developmental improvement in distracter resistance, but since there is maturation in the FEF – IPS network as well, dlPFC is not needed for the improvement of pure maintenance of memories in vsWM.

The quality of our validation that adults were less distractible than children can also be questioned. This was based on the fact that higher activity inside the FEF – SFS network should lead to less distractibility (cf the section *Mechanisms determining task performance – Modeling*). However, we did not test the effect of the developmental increase in dlPFC activity. Study V suggests a mechanism whereby higher dlPFC activity improves distracter resistance. Thus, although our validation is not very strong, it is still comforting that our mechanism did not contradict task performance data.

Another potential problem is that not all connection possibilities were tested. For example, synaptic pruning could have affected inhibitory interneurons more than pyramidal cells, which would cause activity to go up instead of down. On the other hand, it is hard to see how increased fronto-parietal connectivity can be caused by synaptic pruning. Therefore, mechanisms involving changes in inhibitory cells most unlikely caused the observed fMRI data.

Study II – Fronto-parietal connection asymmetry regulates working memory distractibility

Study I and a study by Sakai et al. (2002) had indicated that strong fronto-parietal connections cause improvements in vsWM, but the general structure of the fronto-parietal vsWM network was still unknown. Six possible structural configurations were possible (Figure 12), and we wanted to find out which configuration best reflected the underlying SFS – FEF connectivity. Furthermore, the functional significance of variations in fronto-parietal connectivity was not clear. For instance, was good vsWM related primarily to strengthened connections in the IPS → FEF or the FEF → IPS direction?

We first wanted to determine the asymmetry in the fronto-parietal network. We analyzed the EEG data measured during a vsWM task (same dataset as in study IV). From the data, we used the directed transfer function (DTF; Kaminski et al., 2001)

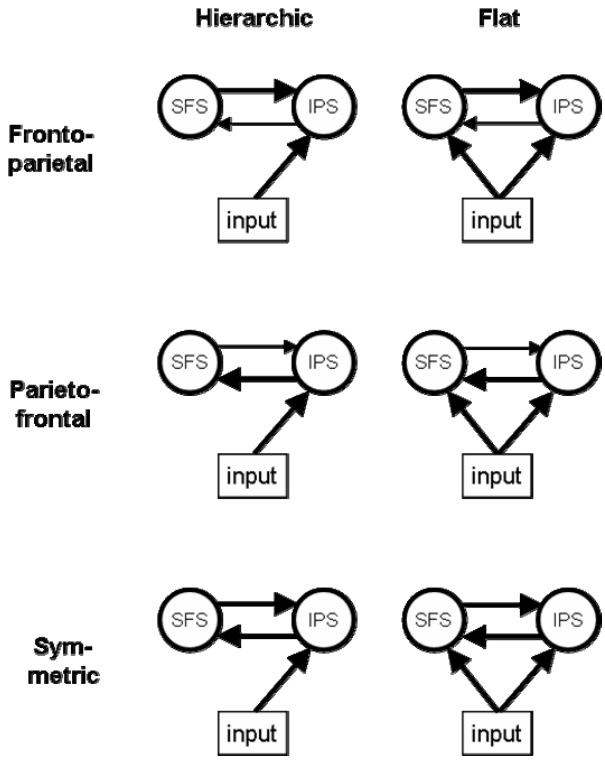

Figure 12. The six possible configurations of the vsWM network. The fronto-parietal network could be either hierarchic (Felleman and Van Essen, 1991) or flat (Chafee and Goldman-Rakic, 1998). FEF→IPS connections could be stronger than, weaker than or have the same strength as IPS→FEF connections.

to measure the effective connectivity[20] between IPS and FEF and vice versa. However, we were not sure how to relate the linear autoregressive model, upon which DTF was based, to maintenance activity in vsWM, which is based on a non-linear mechanism.

Therefore, EEG was simulated from the computational model and simulated DTFs were calculated. After validation and testing of the effect of biophysical factors on the DTF, we could conclude that the fronto-parietal network has stronger connections from FEF to IPS than in the opposite direction. Next, we compared model distractibility to the results of a previous fMRI study (Sakai et al., 2002) to evaluate the hierarchical organization of the network. Simulations showed that stronger network connections only offered protection when the network was hierarchical. We therefore concluded that the vsWM network has strong FEF→IPS connections and that stimuli enter via IPS.

Further simulations showed that this connectivity offers protection against distraction because it creates a buffer system. Stimuli try to enter IPS, but the weak IPS → FEF connections prevent them from reaching FEF, whereas the strong FEF → IPS connections stabilize IPS activity coding for the memory. In addition, we found that strong symmetric connections offer protection against distraction in comparison to weak symmetric connections.

The results of study II provide an explanation for why we saw stronger inter-regional connections in study I. When stimuli enter primarily via IPS, stronger

[20] The effective connection strength from *a* to *b* is the effect that a unit change in activity in *a* has on *b*.

synaptic connections from FEF help to stabilize IPS activity against distracters. This, however, does not imply that the results of study I are due only to strengthened connections in the FEF → IPS direction, since a symmetric increase in fronto-parietal connection strength would also improve resistance. However, increases in FEF → IPS connection strength are especially important for resistance against distraction.

Several factors probably affect our conclusion that the vsWM network is really fronto-parietal, one of which is discussed in study III. At first glance, the most important flaw is presumably the lack of dlPFC in the computational model. dlPFC typically activates when vsWM load is high, which it was in this study (the task difficulty level was adapted in accordance with the WM capacity of each child). However, dlPFC does not seem to be fully mature at the age of 11 (Shaw et al., 2006), which was the age of the children, and children of age 13 do not show any dlPFC activity during the delay or during distraction (Olesen et al., 2007; same data set as study I). This implies that it is more likely that activity in the frontal electrodes really represents FEF activity, as predicted (see the section *How does training improve vsWM?* for further discussion). Another important question is whether we investigated all the biophysical factors that affect the DTF measurements. While the testing of biophysical factors was part of the reason for using the model to establish fronto-parietal connectivity, it is also clear that there could be additional factors to those investigated in study II that might affect the model results.

Study III – Scaling errors in measures of brain activity cause erroneous estimates of neural connectivity

Here I show that measurement errors in the amplitude of neural signals (e.g. through signal attenuation) can lead to miscalculation of effective connectivity measures like DTF, dynamical causal modeling, etc.. The reason is the following: Assume that region a with activity r_a (measured as the amplitude of fluctuations around a mean) connects to region b with connection strength x. Then if a changes its activity by Δ, the activity in b will change by Δx. But if the activity of a is miscalculated (scaled) by a factor f_a, i.e. we falsely measure the activity in a to be r_a/f_a, then the activity change in a, in reality Δ, is measured as Δ/f_a. Since the change in activity in b is still measured to be Δx, we falsely draw the conclusion that the connection strength was $\Delta x / (\Delta/f_a) = xf_a$, i.e. an increase by a factor f_a. The erroneously low (high) estimate of activity caused an erroneously high (low) estimate of connection strength.

But what if activity in b was also scaled by a factor, f_b? Then the activity change in b as a response to activity changes in a will be measured as $\Delta x/f_b$, and the connection strength is estimated as $(\Delta x/f_b) / (\Delta/f_a) = f_a x/f_b$. If $f_b = f_a$, then $f_a x/f_b = x$, the correct value. This means that the bad estimates of the connectivity arise from differences in the scaling factors f_a and f_b.

Since measurement errors are common and often systematically biased in all types of neural data, including fMRI, EEG and multiunit recordings (Simmons et al., 1994, Handwerker et al., 2004), I draw the conclusion that it can be risky to calculate effective connectivity. Instead I present another, related measure, relative influence, which is obtained by normalizing neural data. We know that scaling leads to misestimation of both activity and connectivity. However, when calculating the influence of one region onto the other, i$r_a x$, these two factors cancel each other. So a) we normalize activity (divide activity by its estimated value, which is r_a/f_a and r_b/f_b if there is a measurement error), which b) leads us to draw the conclusion that the connection strength was "change in b" / "change in a" = $[(\Delta x/f_b) / (r_b/f_b)] / [(\Delta/f_a) / (r_a/f_a)] = r_a x/r_b$. So by normalizing, we have produced a lumped measure of all factors

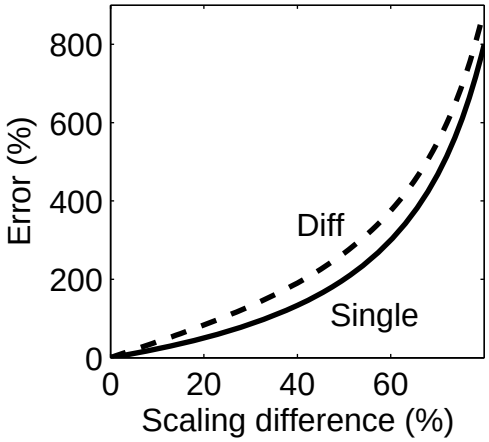

Figure 13. Effect of difference in scaling factor (scaling difference) on connection strength estimation error between two regions. The error of estimation in the strength of a single connection (Single) or the difference between two connections grows dramatically with the scaling difference.

that determine how much a region affects another region. Since the effect of *a* on *b* depends both on the change in activity and on the connection strength, $r_a x$ is a measure of influence. Moreover, since the activity in *b*, r_b, is the sum of all influences on *b*, including the influence from *b* itself, $r_a x / r_b$ is a measure of the influence from *a* on *b* relative to all influences on *b*. We call this measure relative influence.

The new measure also has some advantages, because it does not just measure connectivity, but the total influence that region *a* has on *b* relative to the total variation in *b*. It can be used to arrive at statements such as: "A directional link from *a* to *b* explains 62% of the variability in *b*". Relative influence thus takes into account that the influence of *a* on *b* depends on activity in *a* and not only on the connection strength between the two. Measuring relative influence is easy. The same algorithm used for measuring effective connectivity is used here too, but on normalized data.

My results are very general, and therefore of relevance to most fields of neuroscience and even to other aspects of science. Therefore, it is important to know the effects of errors in effective connectivity. Although connection strengths are affected, the statistical tests for the presence of a connection are still valid. Also, only the estimation of directed connections is affected. Hence, correlations are not affected. However, any precise estimates of connection strength are affected, and any comparisons of two different connection strengths are also affected (Figure 13).

It is possible that the results from study III affect the results from study II. In study II, we normalized the experimental data. Most data from the electrodes are task-irrelevant. If the unrelated data are all of the same magnitude, then the normalization will not have affected the conclusions from the data. However, if this were not the case, then our results will have been contaminated.

Study IV – Alpha synchronization after training of visuospatial working memory in children with epilepsy

Training of vsWM has been shown to improve WM capacity in healthy adults, children with ADHD and adults with brain damage (Olesen et al., 2004, Klingberg et al., 2005, Westerberg et al., 2007). In healthy adults, fMRI activity shows a training effect predominantly in IPS and dlPFC/FEF (The cluster in Olesen et al., 2004 contained both regions). This study asked two major questions:

- Is training also possible in children with epilepsy?
- Was training related to stronger inter-regional connectivity? Study I showed that this was the case during development.

We expected increased synchronization in the α and θ bands, based on previous articles (Krause et al., 2001). We also expected increased coherence, a measure of inter-regional connectivity (Babiloni et al., 1998, Sauseng et al., 2004).

Two main effects were found. Training improved performance in the tested vsWM task, which was, however, very similar to the trained task. Further analyses of the same data set (Persson et al., submitted) showed that training also led to improved performance on the choice reaction time task[21], but not on Raven's progressive matrices[22]. The span board task was not tested.

In the EEG data, we found that activity in the α band increased, but there was no sign of increased inter-regional coherence. Instead, there was a decrease in the β band. The results indicate that mechanisms other than stronger inter-regional connectivity underlie changes in task performance. As shown in study I, one mechanism could be stronger intra-regional connectivity. However, there are many other possibilities, and further studies need to be conducted to understand causes of vsWM improvement. Furthermore, one must be careful when speculating about the effects of the training since the neuropsychological tests in Persson et al. (submitted) only showed generalization to the choice reaction time task.

The data set used in study IV was also used in study II. However, in that study, training effects were not studied. We do not believe that this intervention affected the results of that study in any systematic way.

The etiology of the children with epilepsy was very varying, with some participants having partial and some generalized epilepsy. This is naturally a problem, but at the same time indicates that the results found in this study were probably not related specifically to people with epilepsy, but rather followed a mechanism generally found in children.

Study V – Flexible Prefrontal Bias Signals Regulate Capacity and Access to Working Memory

dlPFC is related to a wide variety of cognitive tasks, including WM, general intelligence and other forms of executive function (Duncan and Owen, 2000). However, executive functions in dlPFC are very poorly understood, despite decades of intensive research. In this study, we

- tested a mechanism for how dlPFC could flexibly control other brain regions during high cognitive demands.
- tested whether this mechanism explains the link between distractibility and vsWM capacity.
- created a simple mathematical equation which explains vsWM capacity as a function of network connectivity.

dlPFC involvement is prominent in vsWM (Sakai et al., 2002). To study dlPFC control of vsWM, we used the vsDR task. dlPFC has been found to activate during high load as well as during distraction. However, these two functions seem unrelated

[21] A complex reaction time task measuring speed with which a simple choice can be made.
[22] A test of general intelligence.

since one is about maximizing the size of the vsWM store, whereas the other one concerns gating the access to the vsWM store. No one has studied these two conditions together before, but from separate studies (Sakai et al., 2002, Olesen et al., 2004), it seems clear that dlPFC is somehow involved in both.

To study dlPFC modulation, we used a vsDR task with instructions to either remember all stimuli (red and blue) or ignore blue (the blue dots functioning as distracters) and only remember red stimuli. We extended our model of the vsDR to implement our mechanistic hypothesis about dlPFC control. The model consists of a visual region, IPS and dlPFC. Each region has two memory networks of the same type, one red and one blue. The red IPS stores the position of red dots and the blue stores the position of blue dots. Unlike the versions of the model used in studies I and II, this version was tuned to store several memories. dlPFC here functions as a source of top-down bias signals. When one of the dlPFC networks activated, it either activated completely or not at all, unlike IPS. This is because nearby and distant excitatory cells have equally strong connections. When the red dlPFC network activated, the red IPS received increased excitatory input, and likewise for blue. Simulations showed the following results (Figure 14):

- IPS has an intrinsic memory capacity, in this case 2 memories (Figure 14A).
- When only the red color region of dlPFC activates, the capacity of the red area is increased at the expense of the capacity in the blue area (Figure 14B), and distracters are filtered.
- When both color regions in dlPFC activate, capacity is increased to 3 memories (Figure 14C).
- Therefore, if dlPFC functions poorly or connections to IPS are weak, performance on both distraction and high memory load tasks would deteriorate. This could explain the link between vsWM capacity and distractibility.

Thus, our mechanism shows flexibility. dlPFC can bias information processing in the posterior brain simply by activating in different ways.

Next, we looked for evidence of this mechanism in dlPFC with fMRI. We found a bilateral cluster of voxels that activated more during high load than low load trials. The same cluster also activated more during distraction tasks. To test the functionality of the cluster, we investigated individual variability and found that higher activity was correlated with better performance in both tasks. Importantly, individuals with higher performance on one task also tended to have higher performance on the other task, confirming model predictions regarding the link between vsWM capacity and distractibility. McNab and Klingberg (in press) found a region in IPS that had higher activity during high load and distraction trials, which could serve as the target of dlPFC modulation. However, distracter-related activity in this region did not correlate with distracter-related activity in our dlPFC region. The significance of this finding is unclear, since IPS activity during distraction should actually be equal or higher during successful (Figure 14A) than unsuccessful (Figure 14B) elimination of distracters in subjects with low capacity, whereas it should be lower in subjects with high capacity (compare Figure 14C to Figure 14B).

Although our evidence supports the role of dlPFC as described by our mechanistic model, it should be kept in mind that other regions of the brain also activated during distracter trials. These regions are shown in Table 3 in the *Discussion* section. Thus, apart from dlPFC, the inferior frontal junction, the inferior frontal gyrus, the insular cortex and the medial frontal cortex were also more active during distracter

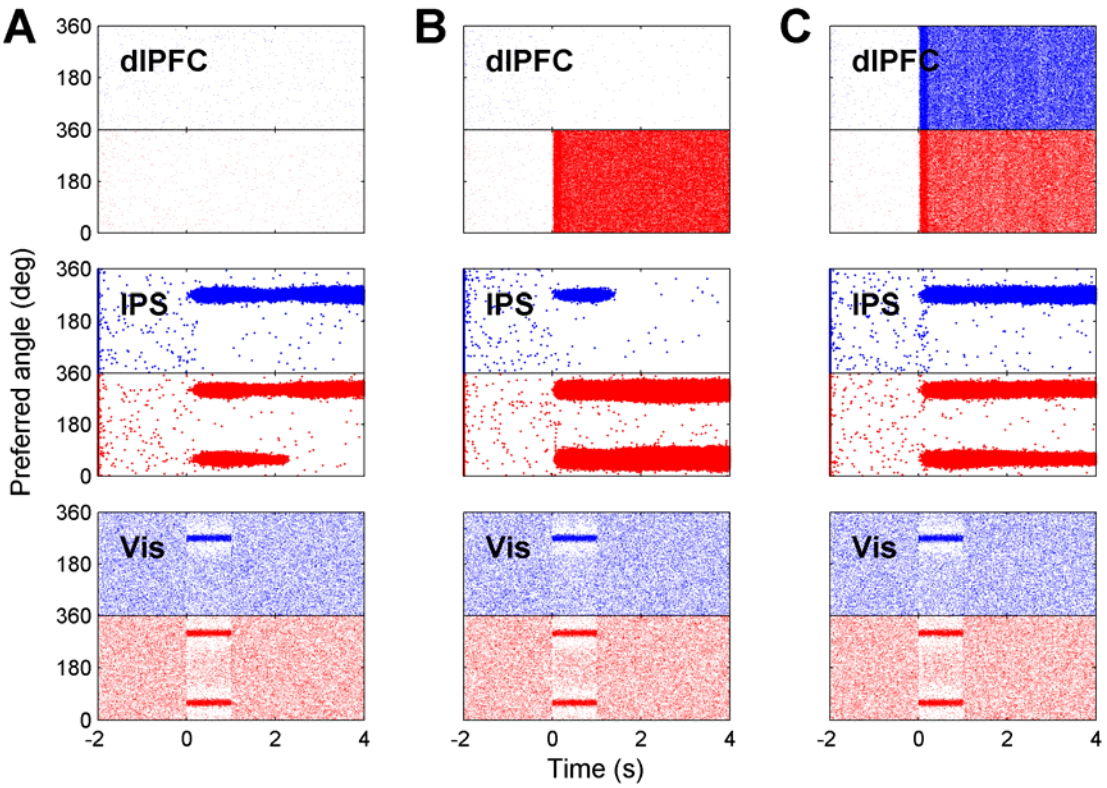

Figure 14. dlPFC modulation of IPS memory activity. Red and blue visual stimuli enter IPS via the visual cortex and are stored. **(A)** Without dlPFC activity, network activity is low, and both distracters and cues are stored. **(B)** When the red dlPFC network is active, excitatory currents into the red population strengthen red activity and render the blue network unable to store memories. Note that total memory activity is higher than in **A**. **(C)** When top-down excitation is given to both color networks of IPS, capacity is increased and three memories are stored.

than during low-load memory trials. These more posterior regions have all been implicated in cognitive control (Bunge et al., 2001, Ridderinkhof et al., 2004, Brass et al., 2005, Feredoes et al., 2006, Hon et al., 2006, Ramautar et al., 2006), but are probably involved in lower levels of sensorimotor processing (Koechlin et al., 2003).

Having found evidence for our mechanism in the brain, we next wanted to evaluate this mechanism in depth. We then performed mean field analysis, allowing the condensation of network behavior into two simple equations. These equations describe the mechanisms setting the capacity limit. The equations showed that:

- As more stimuli are stored in the network, the inhibitory neurons progressively increase their rate. Eventually inhibition is so strong that no more memories can be stored.
- dlPFC increases capacity through excitatory input that counters WM load-dependent increases in inhibition within the memory network setting WM capacity.
- Since there is inhibition between stimuli in the network, selective dlPFC inputs to the red area causes inhibition of the blue area that reduces the capacity of the blue network to 0 memories.

- dlPFC needs to give strong bias signals to IPS to boost capacity, but only weak signals to filter distracters. This means that with limited dlPFC resources, performance on the distracter task should be higher than on the high memory load task.

To test the predictions of the mean-field analysis, we compared performance on the high load task to performance on the distracter task. We found that performance on the distracter task was higher, which confirmed model predictions.

General discussion

In the studies in this thesis, we have investigated neural correlates of and mechanisms determining vsWM performance in various conditions. In addition, in study III I explored a measurement problem that can affect calculations of effective connectivity and complicate empirical testing of hypotheses relating to connectivity.

Two main areas of vsWM performance were investigated. First, we studied mechanisms causing increases in mnemonic activity and capacity (studies I and V). The additional, purely empirical study IV might also be related to the mechanisms explored in study I in a loose way. Second, we tested mechanisms causing improved resistance against distraction (studies II and V).

The studies can also be divided according to the area of investigation. In study I, we studied development, in study IV training, in study V individual differences, whereas the results of studies II and III were general. Another categorization is by brain region. Studies I, II and IV investigated FEF and IPS, whereas study V investigated IPS and dlPFC.

The discussion below is divided more or less into five blocks:

1. I list the main conclusions regarding mechanisms for filtering of distracters and increased capacity/memory stability, as well as a hypothesis regarding neuronal mechanisms underlying the effect of vsWM training.
2. I try to contrast the model to various factors affecting vsDR task performance. This discussion serves the purpose of making it easier for scientists not involved in mechanistic modeling to see the limits of the modeling approach, but also to discuss what the vsDR task can tell us about memory based on brain activity.
3. I try to relate vsWM to other types of WM and general intelligence in order to discuss the generality of the conclusions I have reached.
4. I bring up various limitations of the model that I did not bring up in the summary of the studies. These limitations do not directly question the results of the studies. Rather, they point to improvements of the model that could be made in the future to better relate it to brain activity data.
5. I give suggestions for future studies.

Mechanisms to block distracters

One of the two main areas of investigation in the thesis was resistance against distraction. Three mechanisms were found that lead to improved resistance:

- Study I: Here we studied a network with a capacity of 1 memory. We found that stronger activity led to decreased distractibility. Since the memory store was full after the first memory had been stored, only the stimulus (memory or

distracter) with the strongest activity could survive. Since a distracting stimulus needed to have higher activity than the memory to destabilize the memory, higher memory activity decreased distractibility. This effect presumably also operates when the memory store is full in networks with higher capacity than 1 memory, and was also found in previous studies (Camperi and Wang, 1998, Compte et al., 2000).

- Study II: Connection asymmetry decreased distractibility independently of mean network activity. Distracters were prevented from spreading across the fronto-parietal network by organizing fronto-parietal connectivity so that FEF → IPS connections were stronger than IPS → FEF connections. The weak IPS → FEF connections made it difficult for activity in IPS to influence activity in FEF, and the strong FEF → IPS connections made it easy for FEF to control IPS.

  When the two connections were strengthened by an equal amount, the network became less distractible.
- Study V: dlPFC activity could selectively incapacitate neural populations storing distracters. Memory activity was boosted by excitatory bias signals to memory populations. At the same time, activity in the distracter populations was reduced due to lateral inhibition from the memory populations. The inhibition was so large that memories could not be stored.

In addition, the following mechanism should also operate at lower loads, although this was not tested explicitly:

- Stronger activity should improve the stability of a memory even below the capacity limit. If a distracter (or another stimulus) enters the network and is stored, stronger activity should prevent the memory from spontaneously destabilizing.

The degree of fronto-parietal asymmetry could possibly be measured in subjects with different vsWM capacity, for example with high-density EEG under low-load conditions where dlPFC is presumably not active. The model predicts a correlation between experimentally measured fronto-parietal asymmetry and distractibility.

The aforementioned mechanisms operate during different situations, and offer a multi-layered protection of memories. The first layer of protection is offered by dlPFC top-down modulation. However, when dlPFC is engaged in other tasks, the other mechanisms step in. For example, this could be the case in a dual task (a situation where another, simultaneously performed task takes up resources from dlPFC). If dlPFC is not functional, then connection asymmetry prevents stimuli from reaching FEF. Finally, if distracters eventually reach FEF, then higher activity in FEF prevents distracters from destabilizing stimuli in FEF. Wang and others have studied internal properties of the memory network that render activity stable against distracters, including connection strength, the effect of various interneuronal cell types and the NMDA channel (Brunel, 2000, Compte et al., 2000, Wang et al., 2004).

Interestingly, dlPFC may regulate distracter processing through a combination of the mechanisms presented here. For example, Sakai et al. (2002) showed that dlPFC improves fronto-parietal correlations. Perhaps dlPFC dynamically up-regulates the frontal-to-parietal connection strength when it is needed, in addition to the mechanism explored in study V. By sending bias signals to FEF instead of to IPS, these two mechanisms could be combined.

Network capacity regulation

Studies I, IV and V all found that increased vsWM activity leads to increased capacity. Thus, a basic take-home message from the studies was that increased activity in the fronto-parietal network leads to better performance, which is consistent with previous modeling (Macoveanu et al., 2006) and fMRI/EEG studies (Olesen et al., 2003, Curtis et al., 2004, Olesen et al., 2004, Vogel and Machizawa, 2004). With study V, we can now give a more detailed description of the relationship between activity and performance in vsWM. Any neural structural change that makes G^+ more positive or G^- less negative would improve capacity. This is because these changes would decrease the slope of the line in Figure 7A, 7B so that it stays in the golden area for a longer time. Most of the connections in the model can be changed in this way, which means that there are several ways to increase capacity.

In the mechanistic model, there exists a narrow region where memories can be stored without losing spontaneous activity. The addition of dlPFC control opens up many new questions about how capacity can be optimized without losing stability. A very interesting question to explore would be whether activity in IPS could be regulated such that it always remained in the stable zone, where stability of the memory and no-memory states are both maximized. Figure 7 gives a clue to a solution for this problem, consisting of the following steps:

1. Load another stimulus (upper panel in Figure 7B). This will cause the activity of each stimulus to be lower.
2. Increase input from dlPFC to counter the increased inhibition (lower panel in Figure 7B).

However, evidence for this mechanism would not be easy to find in fMRI, nor with single cell recordings in monkeys.

Study V mainly described one mechanism that sets the network capacity: inhibition. However, another type of network was also used in the study, one with connection tuning between the pyramidal cell and inhibitory interneuron populations. So what is the effect of such a tuning on capacity? Think of the extreme case of tuning, where inhibition from a population of active memory cells is only fed back into itself. In this case, other parts of the network are not affected by activity in that population. Then, if each population can hold one memory, capacity will equal the number of memories. The other case is the one explored in study V. Here, all networks are tightly connected to each other and increasing inhibition sets the capacity limit. Thus, the balance between inhibition and network size for determining capacity is determined by the amount of spatial tuning of feedback inhibition in the network. This indicates the importance of understanding the tuning of the intra-regional connectivity in IPS and FEF.

Other brain regions involved in vsWM

So far in this thesis, only IPS, FEF and dlPFC have been investigated. However, other regions are also commonly associated with vsWM (Figure 6), and in addition, brain regions that are not primarily considered as vsWM regions activated in the studies. In Table 3 below, I summarize the activation patterns in the datasets that were investigated in studies I, IV and V. Not all of the activations observed in study I were

investigated in that study, as a region of interest[23] approach was used, but they were investigated in a companion study (Olesen et al., 2007). Study II shared the same data set as study IV. I will now discuss the role of these regions.

Of the regions presented below, the basal ganglia, thalamus and entorhinal cortex are commonly associated with vsWM, whereas the others are less often associated with vsWM.

Basal Ganglia

The basal ganglia consist of the striatum (caudate nucleus, putamen and nucleus accumbens), the subthalamic nucleus, the substatia nigra pars reticulata and the globus pallidus. This brain region activated in study V (see also McNab and Klingberg, in press). Neurons with persistent activity during the delay-phase of a vsWM task have been found in the monkey basal ganglia (Hikosaka et al., 1989), and the basal ganglia are involved in several functions required for performing the vsDR task, such as stimulus-response learning (Pasupathy and Miller, 2005), response selection (Mink, 1996), planning of complex tasks (van den Heuvel et al., 2003) and gating of access to WM, possibly through a dopamine-regulated switch (Frank et al., 2001). The role of the basal ganglia might be to establish an action selection program in the form of a task set (McNab and Klingberg, in press), possibly maintained by activity in the prefrontal cortex, and changes in striatal activity have been shown to precede those of dlPFC during learning of stimulus-response associations (Pasupathy and Miller, 2005). Cortico-striatal connections emanate from both the frontal and parietal lobes (Parent and Hazrati, 1995), although fronto-striatal connections seem stronger (Leh et al., 2007), but projections back to the cortex via dorsal thalamus almost exclusively target the frontal cortex (Wise et al., 1996). We did not include the basal ganglia in the mechanistic model used in this thesis. The consequences of this choice are unclear.

Thalamus

The thalamus is also active during vsDR tasks, in particular the mediodorsal nucleus (MDN; Funahashi et al., 2004) and the medial nucleus of the pulvinar (Constantinidis and Procyk, 2004). The thalamus was also active in study V. Although little is known about delay-phase activity in the MDN, it is believed to maintain prospective information about saccadic eye movements[24] (Funahashi et al., 2004), a role that fits well with its position in the cortico - basal ganglia - thalamocortical loop, which starts and ends in the PFC (Funahashi et al., 2004), and also with its position in the FEF - superior colliculus – MDN - FEF loop (Sommer and Wurtz, 2001, Sommer and Wurtz, 2006). It is unknown what effect the exclusion of the thalamus from the models in this thesis had on the results. It has connections to both frontal and parietal parts of the cortex (Taktakishvili et al., 2002, Sommer and Wurtz, 2006). On the other hand, the MDN only connects to the prefrontal cortex, including FEF (a definition of PFC is the areas that receive inputs from the MDN (Constantinidis and Procyk, 2004)).

[23] In a region of interest study specific hypotheses regarding the brain areas that are activated are tested. This is in contrast to a whole brain analysis where the whole brain is investigated in an exploratory fashion without necessarily having strong hypotheses about which brain areas are related to the task.

[24] "Saccadic eye movements" or "saccades" refer the rapid eye movements that occur when the gaze is shifted from one object to another, as opposed to the smooth movement of eyes following a moving object.

Entorhinal cortex

The entorhinal cortex has mostly been studied in rodents in tasks that are very different from the vsDR task. The rodents run or swim around in a maze and are required to remember which parts of the maze they have visited (Dudchenko, 2004). However, recent studies in humans and monkeys have found persistent activity during WM tasks as well (Suzuki et al., 1997, Axmacher et al., 2007). Later research has suggested that the hippocampal formation is important for WM when novel stimuli are presented for which a new representation must be formed (Stern et al., 2001, Hasselmo and Stern, 2006), whereas monkeys can still perform WM tasks with highly familiar stimuli after rhinal ablation (Eacott et al., 1994). This indicates that entorhinal activity is not crucial for the performance of the vsDR task, which uses highly familiar dots. It also indicates that synaptic plasticity indeed plays a role even in tasks with very short duration. The entorhinal cortex was not included in the computational models in this study. The effect of the exclusion seems small considering that the stimuli used in experiments were always very familiar. This was confirmed by the fact that the entorhinal cortex was not activated in studies I or V.

Additional brain regions

The following brain regions are normally not associated with vsWM, although some of them often activate in vsWM tasks (see Table 3 for a key to the abbreviations).

SPL: The superior parietal sulcus was generally activated during the delay period of the tasks. This region coactivated with IPS, and it is hard to know whether the two regions constitute one or several clusters. The SPL is involved in spatial attention[25] (Kastner and Ungerleider, 2000), and it has also been activated in studies of intelligence (Lee et al., 2006) and mathematical abilities (Grabner et al., 2007).

IFJ/IFS/PCG/PCSi/SFG: These regions all lie posterior to the MFG and presumably belong to the same functional area as the activations in FEF, since Kastner et al. (2007) found retinotopy in these regions during a spatial vsWM task. Roth et al. (2006) found activity in IFJ in an object WM task and attributed activation to cortical control. These regions were also activated in Klingberg et al. (2002), where the same task was used as in study IV.

FPCi: The inferior frontopolar cortex was activated in study I and the activation lay very near the MFG. As discussed in the *Introduction* section, the FPC is involved in cognitive branching, the process of maintaining a main goal while carrying out subgoals (Koechlin et al., 1999). The role of the frontopolar cortex in the vsDR task is unknown.

IOS/MOG/OC: It is unknown why these occipital regions activated, but it may be due to differences between the main task and the control task. Another reason could be activity due to increased modulation from frontal regions involved in spatial attention (Kastner and Ungerleider, 2000). Sala et al. (2003) found activations in IOS during an object WM task.

aIns/pIns: The insular cortex was more activated in distracter trials both in study I (posterior part) and study V (anterior part). The insula was also activated in a vibrotactile WM study (Sörös et al., 2007). Mayer et al. (2007) and Lepsien et al. (2005) found activity in the insular cortex that correlated with WM load and attentional demands. Scherf et al. (2006) found WM-related anterior insular activation in adults, but not in children.

[25] Spatial attention is a specific type of top-down attention where the focus of attention is a part of the visual field.

Table 3. Summary of the brain regions activated in studies I, IV and V.

Study	Technique	Delay activity[a,b]	Delay activity, development / training	Distracter activity	Distracter activity, development
I[c]	fMRI, ROI[d]	↑: SFS, IFS, PCSi[A], FPGi[A], IPS/SPL, IOS[A]	↑: IPC, SFS, IFS/MFG; ↓: ACG	↑: IPS/SPL, MOG[A], SPL[C], SFS[C], IFS[C], MTG[C], OC[C]	↑: SFS[i], ↓: SFS[i], IFS, ACG, FC, pIns
IV	EEG, Restricted[e]	F_3, P_3	F_3, F_z, P_z	Not applicable	Not applicable
V[f]	fMRI, ROI + WB[g]	MOG, IPL/ SPL, SFG, Th, MeFG, IFJ, IFG, PCG, aIns, LN, MFG	Not applicable	SFG[h], IFG, MeFG, IFJ, Ins, MFG	Not applicable

a) Key to regions: ACG, anterior cingulate gyrus; aIns, anterior insular cortex; F_z, central dorsal frontal electrode; F_3, left dorsal frontal electrode; FC, frontal cortex (near MFG); FPGi, inferior frontopolar gyrus; IFG, inferior frontal sulcus; IFJ, inferior frontal junction; IFS, inferior frontal sulcus; IOS, Intraoccipital sulcus; IPL, inferior parietal lobule; IPS, inferior parietal sulcus; LN, lentiform nucleus (i.e., putamen and globus pallidus); MeFG, medial frontal gyrus; MOG, middle occipital gyrus, MFG, middle frontal gyrus; MTG, middle temporal gyrus; PCG, precentral gyrus; PCSi, Inferior precentral sulcus; pIns, posterior insular cortex; P_z, central dorsal parietal electrode P_3, left dorsal parietal electrode; SFG, superior frontal gyrus: SFS. superior frontal sulcus; SPL, superior parietal lobule; Th, Thalamus
b) Superscripts to areas: A, adults only; C, children only
c) Regions come from a whole brain analysis in Table 1-3 in Olesen et al. (2007). See also the *Results* section in study I regarding SFS activations.
d) Region of interest analysis.
e) Analyses were restricted to electrodes F_3, F_4, P_3 P_4, F_z and P_z.
f) See supplementary Table 4 and the *Results* section in study V.
g) Whole brain analysis.
h) Only frontal areas were investigated.
i) Two different positions. The one that increased with development was anterior, the other one in FEF.

IFG/MTG: These regions are part of the ventral stream and are thought to be implicated in the processing of object or verbal material. On the other hand, Kastner et al. (2007) found retinotopy in the IFG region in a vsWM task. IFG has also been implicated in distracter processing. The regions activated only in study V. Possibly, this could be related to the presence of an instruction cue in the form of a geometric symbol, which was absent in study I.

ACG/MeFG: The anterior cingulate cortex and medial frontal cortex are thought to signal decision conflict (Botvinick et al., 1999, Botvinick et al., 2004, Hampson et al., 2006).

How does training improve vsWM?

vsWM improvements during development and training were investigated in studies I and IV, respectively. In study I, stronger fronto-parietal connectivity was found, whereas study IV possibly indicated training-related intra-regional changes. In what follows, I will hypothesize about possible mechanisms underlying training in vsWM. However, I wish to emphasize that interpretations based on data from study IV must be made while keeping in mind that the generalization effects that we found were

minor. Thus, the training in study IV might only have led to changes in task-specific brain regions.

What could the mechanism for vsWM training be? As described in study IV, one problem associated with the interpretation of the data is that we cannot be sure that the observed frontal activity corresponds to activity in FEF only. On the one hand, it seems reasonable to believe that dlPFC was activated during the delay phase, considering that this cluster was found in the study of vsWM training by Olesen et al. (2004). On the other hand, Olesen et al. (2004) studied adults, and there is a difference between children and adults in that dlPFC does not seem to have vsWM-related activity in children (Olesen et al., 2007). This region is one of the last to develop (Huttenlocher and Dabholkar, 1997), so it is quite possible that it had not developed fully in the children in study IV, who were 2 years younger than in the study by Olesen et al. (2007). It is therefore likely that the frontal task-related EEG changes found in studies II and IV represented activity in FEF. This would suggest that the mechanism behind training might be different in children and adults.

If training-related improvements of vsWM in children might have been caused by intra-regional changes in the FEF – IPS network, what about training mechanisms in adults? Study V suggests that one mechanism could be that dlPFC can provide bias signals to posterior areas more efficiently. So if children and adults differently activate dlPFC, why was no difference in dlPFC activity observed in the developmental study by Klingberg et al. (2002)? After all, we know from the aforementioned fMRI and histological studies that dlPFC matures during adolescence. The difference in results is presumably related to differences in vsWM load in the two tasks. In Klingberg et al. (2002), vsWM load was fixed at a relatively low level, whereas it was higher in Olesen et al. (2004). Developments in the fronto-parietal network could be sufficient to account for most of the increases in task performance in a task with low load. On the other hand, in the vsWM training study, where task load was higher, participants would need to activate dlPFC more to successfully perform the task. Table 4 summarizes my hypotheses regarding group differences between training and developmental effects.

Finally, if Table 4 is correct, how can the increased performance in untrained tasks be understood? In adults, it is clear that training of top-down attention-related activity in dlPFC can explain this. What about in children? One possibility may be activity in FEF. FEF is believed to be important for spatial attention (Awh and Jonides, 2001) and modulates activity in V4 (Moore and Armstrong, 2003), indicating a cross-talk between the ventral and dorsal stream. Thus, FEF activity could lead to better performance on both spatial and object WM tasks. This is clearly just a hypothesis, but if training of a task has resulted in generalization to an untrained task, the training must have led to changes in brain regions that are activated in both of these tasks.

Table 4[a]. Hypothesized mechanisms behind effects of WM training.

	Training, children		Training, adults		Development	
Testing task load	**high**	**low**	**high**	**low**	**high**	**low**
FEF – IPS	↑	↑	↑	↑	↑↑	↑
dlPFC	→	→	↑	↑	↑	→

a) ↑: activity up due to internal plasticity or increased external input from dlPFC. ↑↑: activity up due to internal plasticity and increased external input from dlPFC. →: no change in activity.

The vsDR task revisited

In the *Introduction* section I briefly presented the basic structure of the vsDR task, the main brain regions involved, and the mechanism for maintenance implemented in the mechanistic model. I now discuss in more depth the different components governing performance on the vsDR task. This will better expose which parts of the vsDR task that can be understood by studying the computational model, and vice-versa, and what individual differences in performance on vsDR tasks tell us about mechanisms for memory retention.

The basic requirements for a memory are encoding, retention and memory retrieval. As partly described in the *Functional Anatomy of vsWM* section, these three functions are handled by the fronto-parietal vsWM network. However, in addition to the bare retention of stimuli, task performance is affected by a range of factors, some of which can be varied in the task design.

Dual tasks: A major endeavor is to understand the contributions to task performance from the "bare-bones" memory network vis-à-vis the attached dlPFC modulatory control region. This can be done with a dual task (Kane and Engle, 2002): if two memory regions share a control system, simultaneous performance in one task should reduce performance in the other.

Manipulation: Another method that gives essentially the same result as the dual task requires subjects to perform a manipulation on the data, such as reciting a memorized sequence backwards. Manipulations have been a very common feature of human behavioral WM research. In fact, the most common definition of WM is the "ability to temporally retain and manipulate information" (Baddeley, 1974, Baddeley, 1998), although this is not the definition used in this thesis.

Chunking: Another factor is the type of representation of memories. Chunking is the process of associating two pieces of information in order to reduce memory requirements (Gobet and Simon, 1998). For instance, the "3" and "1" in "31" can be maintained separately, or they can be chunked into "31" if that facilitates task completion. The vsDR task is designed to make chunking difficult, but chunking is still often used (Ridgeway, 2006), although it is more probable if there is a natural association between two or more stimuli (Fendrich and Arengo, 2004). Chunking can be regulated by the choice of presented stimuli, and it may also be possible to partly prevent chunking by shortening the presentation time (Fendrich and Arengo, 2004).

Rehearsal: The rehearsal of memoranda also improves task performance. Verbal memoranda are often rehearsed subvocally (Baddeley, 1986), whereas memories of locations are often rehearsed by sequentially shifting the attentional focus to all the locations that are to be remembered (Awh and Jonides, 2001). To prevent rehearsal, subjects may be required to repeatedly say a syllable out aloud (Murray, 1968) or move their eyes or their focus of attention in a predefined manner (Lawrence et al., 2004). Spatial attention is dependent on activity in FEF, the superior parietal lobule and the supplementary eye field, regions which are also involved in the generation of saccadic eye movements (Kastner and Ungerleider, 2000).

Distracters: Distracters were described in the *Introduction* section and earlier in the *Discussion* section. Distracters are usually presented either at the same time as the stimulus or during the delay period.

Lures: In some versions of the vsDR task, the subjects do not indicate the location of the stimulus themselves, but respond to a yes/no question of the form: "Was the stimulus presented here?" In the trial presented in Figure 15, there was a dot in the grid position adjacent to the question mark, which can confuse subjects and cause them to respond incorrectly. This type of trial is called a lure trial, although that

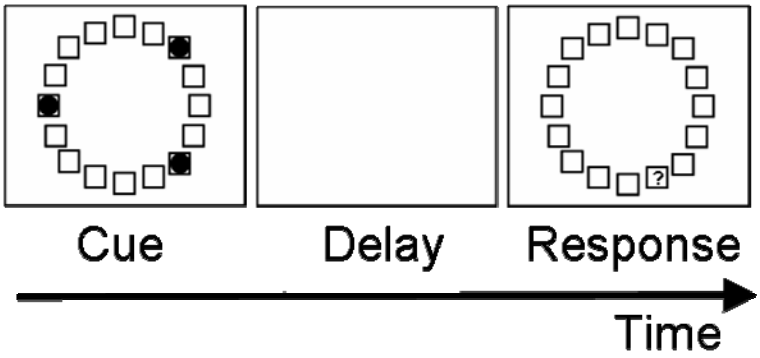

Figure 15. A lure trial. The subject is questioned about the presence of a dot at the location of the question mark. The question mark is adjacent to a position which had previously been filled with a dot, which increases the likelihood that subjects respond affirmatively (but incorrectly).

term is mostly associated with the *n*-back task, which is slightly different from the vsDR task. It has been shown that performance on lure trials in the *n*-back task depends on activity in dlPFC and is strongly correlated with general intelligence (Gray et al., 2003).

Presentation time: Stimuli may either be presented simultaneously or sequentially and presentation time can vary. The time allowed for stimulus encoding seems to affect task performance (Vogel et al., 2006). This could possibly be caused by perceptual factors related to the attentional blink (Vogel and Luck, 2002), or to the time it takes to find an optimal representation of the memory through various mechanisms such as chunking (Fendrich and Arengo, 2004). Little is known about the neural processes governing chunking and encoding. For this reason, stimuli are usually kept as simple and as hard to relate to each other as possible in order to avoid strong effects of chunking and encoding strategies on behavior and brain activity.

Consequences for mechanistic modeling

Given the importance of active memory and its modulation in the vsDR task, it is very important to obtain a mechanistic understanding of factors governing task performance. Until recently, the focus of the modeling has been to investigate the stability of persistent activity *per se* as a function of structural and activity characteristics such as connection strength, degree of activity synchronization and mean firing rate (Compte et al., 2000, Tegnér et al., 2002, Wang et al., 2004). The amount of drift of memory activity has also been the topic of some research (Compte et al., 2000). Apart from these very basic aspects of the task, only distractibility has received a lot of attention, and two of its mechanisms have previously been explored (Compte et al., 2000, Wang et al., 2004). In this thesis, factors regulating distractibility were further investigated, especially in studies II and V. Study V is particularly relevant, since it is one of the first biophysically based vsWM models that tries to model the flexible dlPFC activity thought to account for most of the correlation between vsWM and general cognitive abilities (see also Deco and Rolls, 2005). Hopefully, more of the aspects governing task performance that were mentioned above can be included in the model.

For several reasons, studying vsWM is also important for the general understanding of active memory. vsWM tasks are presumably culturally neutral and ideal for comparison across species, meaning that a rich source of knowledge about

the neurophysiology and histology of vsWM-related brain regions is experiments in macaques (Goldman-Rakic, 1995). In addition, since vsWM tasks do not involve vocalization of the information that is to be remembered, language structures in the brain are not involved as much as they are in verbal WM tasks, which makes it easier to generalize the findings to other types of active memory.

At the same time, it must be remembered that all the factors presented in the section *The vsDR task revisited* affect the performance on the vsDR task, which means that individual differences in task performance can arise for reasons other than differences in pure active memory.

Other mechanisms for maintenance via persistent activity

So far, variants of active memory other than vsWM have not been discussed. However, memory based on persistent neuronal activity is a very general phenomenon that does not only subserve maintenance in vsWM, but also a collection of other processes ranging from sustained attention in primates to activity in the stomatogastric ganglion of the crab[26] (Major and Tank, 2004). Therefore, mechanistic knowledge about persistent activity in vsWM can be gained by studying models from other systems too, just as the results from this thesis might be applicable to other types of active memory. An example of a shared mechanism is the one between WM for fluttering tactile stimuli and oculomotor control circuits in the brainstem (Major and Tank, 2004).

Most theoretical models of persistent activity in WM assume that activity is stable, i.e. if nothing interrupts it, it would persist indefinitely. This is based on the idea that synaptic time scales are too short to generate currents that span the whole delay in a DR task. However, several factors indicate that stable persistent activity may not represent the whole picture of WM. For example, quite a lot of temporal dynamics have been found during the delay period of WM tasks, with neurons ramping both up and down (Durstewitz et al., 2000, Fuster, 2001, Major and Tank, 2004). Thus, although stable persistent activity is the most explored mechanism behind WM, other possibilities also exist.

There are several kinds of model of stable persistent activity in WM, each of which has been developed for a specific biological system and task (Durstewitz et al., 2000, Wang, 2001, Brody et al., 2003, Compte, 2006). In Table 5, three basic categories are described. These are based on the basic representation of memories in the model, but there are also other ways to categorize the models. For instance, categorizations can be based on the mechanism of persistent activity, such as through recurrent synaptic transmission (Compte et al., 2000), intracellular Ca^{2+} (Fransen et al., 2006), short-term synaptic plasticity (Sandberg et al., 2003) or after-depolarization (Jensen et al., 1996).

Table 5 shows that WM for objects and vsWM presumably share the same mechanism, whereas WM for cutaneous vibrations (flutter) is based on another mechanism. This means that the results in this thesis could generalize to object WM. It is important to keep in mind that "the map is not the territory": the vsWM model usually only employs one mechanism for persistent activity, recurrent excitation, but other mechanisms might also play an important role. One such mechanism is cellular bistability (Camperi and Wang, 1998), the most important mechanism for various types of graded persistent activity.

[26] Even this type of persistent activity can be viewed as one form of memory, because the state of activity of this ganglion at a point in time gives information about its past state.

Table 5. Classes of models for WM-related persistent activity.

Model type	Representation	Mechanisms	Memory systems
Hopfield models[a]	Activity in cells coding for stimulus	i, ii, iii	Cortical object and vsWM
Graded activity models[b]	Stimulus coded in rate of persistent activity	i, iii, iv	Flutter discrimination, entorhinal graded act.
Jensen-Lisman[c]	Phase in firing cycle	v	Hippocampus

i) Strong local recurrent synaptic connections stabilize increased activity.
ii) Same as i), but with short-term plasticity causing the connection profile.
iii) Increased intracellular currents causing cellular bistability.
iv) Monostability, but with fixed point adjusted by $[Ca^{2+}]$.
v) After-depolarisation.
a) (Amit and Brunel, 1997, Camperi and Wang, 1998, Fransen and Lansner, 1998, Lisman et al., 1998, Wang, 1999, Compte et al., 2000, Wang, 2001, Tegnér et al., 2002, Macoveanu et al., 2006)
b) (Robinson, 1989, Koulakov et al., 2002, Brody et al., 2003, Fransen et al., 2006, Hasselmo and Stern, 2006)
c) (Lisman and Idiart, 1995, Jensen et al., 1996, Jensen and Lisman, 1996, Jensen and Lisman, 1996)

Relation to other cognitive abilities

In the last section, I discussed the generality of my results based on mechanisms for the retention of information as well as its representation. However, there are additional ways that vsWM is related to other cognitive abilities. A relevant categorization of a cognitive function is the modality/type of information on which it operates, because different neural circuits with different characteristics encode different types of information. Thus, visuospatial WM performance should be indicative of other spatial abilities, while at the same time it is theoretically possible for a person to have a different WM capacity for different types of WM.

vsWM can also be indicative of other cognitive abilities because of shared modulation systems, such as dlPFC activity (Duncan et al., 2000, Kane and Engle, 2002). Study V indicated a possible mechanism whereby individual differences in vsWM can be related to distractibility: they shared the same control system.

Interestingly, the vsDR task is linked to problem solving abilities and general intelligence, more so than similar tasks for other forms of STM[27] such as STM for verbal information (Kane et al., 2004, Kane et al., 2007), probably because it makes use of dlPFC activity to a larger extent than verbal vsSTM tasks (Kane and Engle, 2002). Performance on vsDR tasks should therefore be predictive of other types of memory that also depend on prefrontal activity to a large extent.

Not only changes in dlPFC but also improvements in the "bare-bones" capacity of the fronto-parietal network itself could indirectly affect the outcome measures in memory-dependent cognitive tasks. A highly functioning fronto-parietal network demands less top-down resources from dlPFC, which is then free to carry out other cognitive operations.

Since top-down attention / cognitive control is strongly related to the general cognitive abilities of a person, it is interesting to note recent studies describing an architecture of cognitive control in the frontal cortex (Fuster, 2001, Koechlin and Summerfield, 2007). These results clearly have relevance for cognitive training. The

[27] Some tasks are considered to be STM tasks, since they are presumed to require less top-down attentional resources. However, no pure STM task exists.

tasks that have already been used to map out this frontal architecture could also be used for diagnostic and training purposes. After finding dysfunctional brain areas that underlie the cognitive deficits of a person, the appropriate training task involving those areas could be designed to alleviate the symptoms of that person.

vsWM model assumptions

Every model is based on assumptions. The vsWM model is based on many. Therefore it is important to understand the effect of errors in these assumptions. I will now discuss two of the assumptions made in the model that were not mentioned above.

Parameter values

The model is very underdetermined. This means that even if many of the qualitative statements about the model are correct, quantitative statements may be hard to make. This makes it difficult to use the model to compare the relative effect of various mechanisms. Study II could suffer from this problem. As pointed out in that study, several factors could affect the relationship between the underlying neural activity and the DTF. While this served as the rationale for using the model to establish fronto-parietal connectivity, it is also clear that there could be additional factors to the ones investigated in study II that might affect the model results.

The mechanism behind activity in the no-memory state

Cortical cells show a spontaneous activity even in the absence of stimulations. A major effort in the development of this model has been to replicate this activity, and the possible model parameter values are strongly restricted because of this requirement. This has resulted in model fragility that poorly matches common notions about biological robustness. More energy is therefore needed to understand why high spontaneous activity can be stable. It is possible that facilitating and adapting synapses could be a stabilizing factor (Barak and Tsodyks, 2007).

Model complexity

A good model should be parsimonious yet flexible enough to explain observed data (Herz et al., 2006). During this whole thesis, a problem has been that the computational model is the opposite. In monkey cortex, there are three types of cells coding for cue, delay and response (Funahashi et al., 1989). Yet the model only contains delay cells, which means that we can only model the delay phase of vsWM experiments. On the other hand, there is a variety of cellular complexities built into the model (in studies I,II) that generally cannot be studied in fMRI experiments.

Model complexity should thus be matched to data complexity and to the question of interest. We have often talked about the usefulness of creating a range of models of various complexities, with simpler models consisting of several brain regions for comparison with fMRI data, and more complex models for the study of various biophysical details, such as the effect of drugs on behavior.

The mean field model formulated in study V takes the first step towards this hierarchy of models. With the model, tedious simulations can be avoided, and theoretical understanding can more easily be extracted. In the future, the mean field model should be expanded to encompass more brain regions, e.g. FEF. The feasibility of this approach depends on the uniqueness of different regions of the brain. Although each region in the brain is unique, it is also commonly believed that the similarities are greater than the dissimilarities (Mountcastle, 1997), which is also shown by the

apparent similarity in information processing between areas at the very top of the cortical hierarchy and those at the bottom (Koechlin et al., 2003).

Cortical connectivity

The thesis shows the importance of network connectivity for vsWM function, but also that appropriate statistical models are needed for analyzing connectivity. Study II is the best example of this, because in this study, there were functional differences that were not associated with either changes in activity or correlations, and which therefore would not have been discovered unless the strengths of directed connections (effective connectivity) were measured. It is therefore important that reliable methods for directed connectivity be developed. Study V is another example. Without the model, one might draw the conclusion that the training effects in IPS and dlPFC that were found in Olesen et al. (2004) are due to changes in both regions, whereas study V suggests the possibility that changes only occur in dlPFC.

Study III discusses some of the pitfalls with measuring effective connectivity. Another problem that is general for effective connectivity methods such as dynamic causal modeling and structural equation modeling in WM is that they are linear (Friston et al., 2003, Horwitz, 2003). The very basis of a memory is that there can be at least two stable states, even when there is no external input. This is only possible in non-linear models (Friston, 2001), because linear models can only have one stable state. This implies that model fitting will give unpredictable results unless a linearization around one of these states is done (i.e., one only looks at fluctuations around either the memory or no-memory state) by cutting out time segments corresponding to each of these states and doing model fitting on each of these. This was done in study II, where the model was fitted to delay period activity only or delay phase activity only. Unfortunately, this type of analysis is impossible to perform with fMRI due to the low sampling frequency and slow time constant of the hemodynamic response function.

Given the importance of connectivity, this calls for the development of non-linear models, preferably with a biophysical foundation but still with only a few parameters to reduce the amount of data needed for estimation (Friston, 2001). Perhaps the mean-field model developed in study V could serve as a basis for such a development. However, the development of such models and the accompanying experimental protocols will be a tremendous task, because to understand vsWM network connectivity, we would not only need the appropriate statistical models, but also the ability to perturb the vsWM system. To date, this has only been possible by variations in the task (distracters, rule changes, etc). Perhaps, it will be possible to develop protocols for controlled intervention with transcranial magnetic stimulation[28] or similar techniques in the future.

Future studies

The research here, especially from study V, opens up a whole range of possible future studies. In addition to what has already been mentioned earlier in the *Discussion* section, I here describe a few ideas that have sprung to mind during these five years as a PhD student. Generally, these ideas fall into two categories, either to test the

[28] A technique where a magnetic pulse applied outside the head crosses the skull and affects electrical activity in the underlying brain tissue. This technique can induce reversible and temporary dysfunction of the brain region or lead to a short surge of electrical signaling that can spread to connected regions. It is considered harmless under most circumstances.

existing parts of the model by doing experiments testing model predictions of performance, or to expand the model to cover more of the vsWM network.

Forgetting curves

To test the mechanisms of memory accuracy, forgetting curves can be simulated and tested behaviorally with an oculomotor delayed response task. Based on model predictions, we would expect two possible situations.

- Errors are mostly caused by network activity reverting to the no-memory state: In this case, drift would be low, and the model would have a constant probability over time of switching to the no-memory state. This would produce a proportion of trials with accurate responses and a proportion with responses evenly distributed across the visual field. The proportion of accurate trials would decay exponentially.
- Errors are mostly caused by drifting network activity: In this case, trials would not be separable into two classes. Instead, the variance of responses would increase over time. The temporal characteristics of this type of decay are not totally predictable from the model because of model differences arising from the use of different cell types (Hodgkin-Huxley or integrate-and-fire) and the temporal correlation patterns in the external driving current. In the integrate-and-fire model with Poisson distributed external driving, the variance of responses increases linearly, suggestive of a diffusion process (Compte et al., 2000).

Surprisingly little research has been done on forgetting curves. Wickelgren (1969) and Klingberg (1997) found exponential decay in an auditory WM task, supporting memory instability as a mechanism for decay. On the other hand, other researchers have found some support for the drift as a main cause of errors in humans performing the oculomotor delayed response task (Funahashi et al., 1989, Ploner et al., 1998). With the model, a systematic exploration taking into account the effect of vsWM load could be done. This would be a strong test of the mechanism behind persistent activity as suggested in the model.

Overlapping memories

Research on associative long-term memory suggests that memories are stored through plasticity in the synaptic matrix in much the same way as in the present models of vsWM (Hopfield, 1982). The main differences are that memories are overlapping in models of associative memory, which leads to increased storage possibilities, and that they have clearly defined energy minima, which means that there is no drift. Now that models that can store multiple memories exist, we can create corresponding models of object WM with overlapping memories to explore factors setting the capacity limit in this type of memory. The following factors could be explored:

- The degree of overlap: Can two overlapping memories be active at the same time? How much can they overlap?
- Synaptic plasticity: Synaptic plasticity could be a larger contributing factor to memory stability in object WM than in vsWM given that semantic and emotionally salient objects often lead to fast synaptic plasticity. Mechanisms for synaptic plasticity can be built into these models and studied. By studying forgetting curves, it could be possible to see how fast these mechanisms set in.

This could give us an understanding for the interplay between long-term memory and short term memory.

The different roles of FEF and IPS

The core brain regions in the vsWM network in this thesis are FEF, IPS and dlPFC. As shown in experiments (Kastner and Ungerleider, 2000, Curtis and D'Esposito, 2003, Curtis et al., 2004), FEF is involved in spatial attention and seems to employ a prospective/motor code for solving the vsWM task, whereas IPS uses a retrospective code. It would be interesting to create a model that separates the behavior of these two regions and test this with appropriate experiments. However, since prospective coding and saccade generation seem to require subcortical areas such as the mediodorsal nucleus of the thalamus (Funahashi et al., 2004, Sommer and Wurtz, 2006), these regions may need to be included in such a model.

The attentional blink

Marois (2005) has identified three major capacity limiting steps of information processing in the human brain: the attentional blink, STM capacity and the psychological refractory period. The attentional blink is a capacity limit in explicit visual event detection. Subjects can only detect up to about 4 stimuli instantly in their spatial focus of attention. After encoding of an array of visual stimuli, participants will be severely impaired at detecting stimuli presented during the following 500 ms (Raymond et al., 1992), and also at consolidating them in memory (Vogel and Luck, 2002). The visual capacity limit is strikingly similar to the capacity limit of the vsDR task as reported by Cowan (2001) and Luck and Vogel (1997). This suggests that estimates of the STM capacity limit could be influenced by a perceptual bottleneck. Suggestive of such a mechanism, previous studies in the Developmental Cognitive Neuroscience group having longer encoding periods have suggested that the capacity limit of STM is higher (Olesen et al., 2004, Klingberg et al., 2005). So far, no one has performed a rigorous psychophysical study of the dependence of STM capacity on presentation time for times above 500 ms, although Vogel et al. (2006) tested this for shorter times.

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