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WORKING MEMORY: DEVELOPMENT, DISORDERS AND TRAINING

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ABSTRACT

Working memory: Development, Disorders and Training

Working memory (WM) is the ability to keep information online during a short period of time. Brain regions underlying WM functioning are found in the frontal and parietal cortices. It is largely unknown to what extent the neural substrates underlying WM are susceptible to training induced change. Here we investigate the development of WM capacity, if improvement by training is possible and explore the neuronal correlates for training induced change.

In Study I we used functional magnetic resonance imaging (fMRI) to investigate the neural correlates of the developmental change in WM capacity during childhood. We found that during performance of a visuo-spatial working memory test (VSWM), there was a significantly higher activity in the superior frontal and intraparietal cortex in subjects with higher capacity. Thus, the development of these areas may underlie the development of VSWM during childhood. In Study II we used the VSWM test in children with and without ADHD and found that the test differentiated between these groups ($P<.01$). This supports the hypothesis that the WM deficit is a core deficit in ADHD. We proceeded by investigating if it was possible to improve WM capacity by training on WM tasks and secondly, if training effects could generalize to other cognitive tasks and areas of behaviour. These hypotheses were tested by designing a computerized program for WM training which was implemented in children with ADHD in two consecutive studies. In Study III (N=14), we saw significant improvements in the treatment group as compared to the control group on the trained WM task ($P < .001$), on the non-trained WM tests (span-board $P < .001$, and digit span $P < .001$), as well as on other non-trained tasks; Stroop ($P < .01$) and Raven's matrices ($P < .001$). In Study IV the effects on the cognitive tests were replicated at a significance level of .01, with a randomized, double-blind, placebo-controlled multi-center design (N=44). In this study we also found generalisation of training effects to the behavioural level as evaluated by parents and teachers (inattention $P < .01$) and parent-rated hyperactivity/impulsivity $P < .05$). In Study V we investigated if stroke patients with significant WM deficits also could benefit from training. Participants suffering stroke one to three years earlier gained significant improvements in WM capacity (digit span $p < .005$, span board $P < .05$, and PASAT $P < .001$), and attention (RUFF 2&7 $p < .005$), as well as on cognitive symptoms in daily life, as measured by a self rating questionnaire ($P < .005$). Study VI was undertaken to explore the neuronal correlates of WM improvement. Healthy young adults underwent fMRI before and after WM training. Task specific increases in brain activity were found in prefrontal and parietal cortices. These regions are known to underlie WM functioning.

In summary: WM shows a prolonged developmental course in humans. WM deficits are prominent in ADHD and following brain injury. WM can be improved by training and the training effect also generalizes to other cognitive tasks. The increase in WM capacity during childhood as well as after training is associated with increased brain activity in the prefrontal and parietal cortices.

LIST OF PUBLICATIONS

I. Klingberg T, Forssberg H, Westerberg H
Increased Brain Activity in Frontal and Parietal Cortex Underlies the Development of Visuospatial Working Memory Capacity during Childhood
Journal of Cognitive Neuroscience, 2002, 14:1, pp. 1–10

II. Westerberg H, Hirvikoski T, Forssberg H, Klingberg T
Visuo-spatial working memory span: a sensitive measure of cognitive deficits in children with ADHD
Child Neuropsychology, in press

III. Klingberg T, Forssberg H, Westerberg H
Training of Working Memory in Children With ADHD
Journal of Clinical and Experimental Neuropsychology, 2002, 24:6, pp. 781-791

IV. Klingberg T, Fernell E, Olesen P, Johnson M, Gustafsson P, Dahlström K, Gillberg CG, Forssberg H, Westerberg H
Computerized Training of Working Memory in Children with Attention-Deficit/Hyperactivity Disorder – a Controlled, Randomized, Double-blind, Trial
Submitted

V. Westerberg H, Jacobaeus H, Hirvikoski T, Clevberger P, Östensson M-L, Bartfai A, Klingberg T
Computerized Working Memory Training - A Method of Cognitive Rehabilitation after Stroke
Submitted

VI. Olesen PJ, Westerberg H, Klingberg T
Increased prefrontal and parietal activity after training of working memory
Nature Neuroscience, 2004, 7:1, pp. 75-79

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
BOLD	Blood Oxygen Level Dependent
CNS	Central Nervous System
CPT	Continuous Performance Test
CRT	Choice Reaction Time
DMS	Delayed Match to Sample
DLPFC	Dorso-lateral Prefrontal Cortex
DSM-IV	Diagnostic and Statistical Manual of mental disorders, 4th ed.
DTI	Diffusion Tensor Imaging
EEG	Electro-Encephalography
ES	Effect Size
fMRI	functional Magnetic Resonance Imaging
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
PFC	Pre Frontal Cortex
SPM	Statistical Parametric Mapping
STM	Short Term Memory
TBI	Traumatic Brain Injury
TMS	Trans cranial Magnetic Stimulation
WM	Working Memory
VSWM	Visuo Spatial Working Memory

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1 GENERAL INTRODUCTION

1.1 DEFINITION OF WORKING MEMORY

There are many definitions of WM stemming from different areas of research, from psychology (Alan Baddeley) to neuroscience (Patricia Goldman-Rakic). Since our work is in the field of cognitive neuroscience we have used definitions close to Goldman-Rakic´s (1987) definition; "Working memory is the ability to keep information online during a short period of time". However, our view of WM also agrees on a broader description of WM, which includes operations on the information held on-line.

1.1.1.1 Background

Working memory is close to and sometimes partly overlapping with other cognitive constructs, as for example short term memory (STM), attention, executive functioning and interference control (see these paragraphs respectively for a more detailed description). To put it short; WM includes the selection of relevant information to attend to and the filtering out of irrelevant information, functions that also can be described as Control of Attention, (Engle RW, Kane JM & Tuholski SW, 1999).

The term "working memory" was introduced into the literature of cognitive psychology by Miller, Galanter and Pribram in their book *Plans and structure of behaviour*, 1960. Their definition is astonishingly modern; they did foresee the goal directed and executive components of WM:

"*When we have decided to execute some particular plan, it is probably put in some special state or place where it can be remembered while it is being executed. Particularly if it is a transient, temporary kind of plan that will be used today and never again, we need some special place to store it."…"…we should like to speak of the memory we use for the execution of our plans as a kind of quick-access, working memory*." (p.65)

They did not stop with a cognitive definition of working memory, but went on and proposed an anatomical localisation of these functions in the brain:

"*This most forward position of the primate frontal lobe appears to us to serve as "working memory" where plans can be retained temporarily when they are being formed, or transformed, or executed*." (p. 207)

According to my own opinion the functional purpose of WM is to guide goal-directed thoughts and behaviour. The ability to maintain sensory representations no longer present in the environment, and piece together relationships between these and internal information is a prerequisite for goal-directed and adaptive behaviour.

Since the fifties there have been a number of definitions of WM and STM, often describing the same cognitive construct (see §1.4.1 *Short term versus working memory*). The term STM was more often used earlier while the term WM has successively become more common and are the most frequently used today. These concepts have been incorporated in such disparate areas as psychology and computer programming (Shute VJ, 1991). In spite of the lack of an agreement on a core-definition of WM, shared in different nomenclatures, most definitions of WM include components of temporary storage of internal representations (maintenance), operational processes (manipulation) upon these, and some definitions also include (executive) control aspects. Furthermore, WM has been fractionated into different basic subcomponents. Terms often encountered are listed below.

Content The representations temporarily held on-line during the delay of WM tasks consists of either external information from the sensory system, or internally stored information, retrieved from long-term memory (LTM).

Process The content in WM is not only maintained (which is more in line with the definition of STM) but can be manipulated by different operations, with the prospective aim of facilitating goal directed behaviour (external as motor execution or internal such as decision making).

Rehearsal One way to actively maintain the information in WM is to rehearse it, (repetitively direct attention to it). Rehearsal supports WM, protects the information from fading and possibly also from interference from competing stimuli (Raye CL, Johnson MK, Mitchell KJ, Reeder JA & Greene EJ, 2002).

Decay The content in WM is retained transiently (for seconds) and is not stored in LTM. If not actively maintained (repeatedly attended to), the content vanishes.

Interference control The ability to inhibit attending to irrelevant information influences how well the relevant representations can preserve against passive decay and distracters.

Capacity Capacity is a quantitative value that describes the maximum amount, i.e. the number of items of information that can be held active in parallel in WM. WM capacity corresponds to an individual's current ability or to the average ability of a defined population such as an age group. The capacity of WM is limited and a popular view is that seven (±2) items of information can be processed simultaneously in WM. Although, one item can constitute a ´chunk´ of information; a chunk is a cluster of logically connected items, maintained as one and thus extending the perimeter of seven. A concept closely related to WM capacity is *WM Span* which denotes the upper limit an individual manage to reach on a particular WM test.

Load effect Quantifies the relative processing resources required to perform a WM task. The load on WM is not only about the number of items to be maintained, but can also denote the need for elevated processing in for example performance of dual tasks (see §1.4.3).

1.2 NEURONAL MECHANISMS UNDERLYING WORKING MEMORY

Research in the field of WM is quite unique in that it spans from sub cellular mechanisms such as the function of dopamine receptors in neurons, via neuronal networks, over cognition to the behaviour level (Goldman-Rakic 1995, 1996; Castellanos FX & Tannock R, 2002). The neural substrates of WM in both primates and humans is found in the prefrontal cortex (PFC); recorded at the neuronal level during delay-specific activity in primates (Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster & Alexander, 1971; Tsujimoto S & Sawaguchi T, 2004) and documented by neuro-imaging methods at the cortical level in humans performing WM tasks (Jonides J, Smith EE, Koeppe RA, Awh E, Minoshima S & Mintun MA, 1993; Courtney SM, Petit L, Maisog JM, Ungerleider LG & Haxby JV, 1998a; Paulesu E, Frith CD & Frackowiak RS, 1993; Cohen JD, Pearstein WM, Braver TS, Nystrom LE, Noll DC, Jonides J & Smith EE, 1997). In the search for the neuronal mechanisms that underlie WM, tasks that tap vision are most commonly used in primates since they lack language. A frequently used paradigm in animal research is the delayed match to sample (DMS) task, in which for example a piece of food is placed in a container by an experimenter while the monkey watches. During the delay a cover is applied which prevents the monkey from visually fixate the containers. After the delay the cover is removed and the monkey indicates in which container it thinks the food is. Also in humans a great deal of research utilizing brain imaging techniques has focused on non-verbal WM. One reason is the intent to compare and extend the findings from animal studies. Another reason is that at least magnetic resonance imaging (MRI) is noisy and can interfere with auditory WM tasks. In human's, tasks similar to but more demanding than the DMS has been used, for example the N-back test, in which the subject has to match and respond to stimuli that appeared one, two or three items back in a series. The delay specific activity seen in electrophysiological single cell recordings in the PFC of primates (Funahashi, Bruce, & Goldman-Rakic, 1989) are thought to be analogous to the delay-specific activity found in functional brain imaging studies in the PFC of humans (Cohen JD, et al., 1997; Courtney SM, et al., 1998a; Rowe JB, Toni I, Josephs O, Frackowiak RS & Passingham RE, 2000)

1.2.1 Working memory at the cellular level

Work with electrophysiological recordings in awake monkeys shows that neurons normally change their rate of firing when a distracting stimulus that interfere with ongoing activity appears (Miller EK, Erickson CA & Desimone R, 1996). But there are some areas of the brain, situated in the PFC where neurons maintain their rate of activity, induced by holding a target stimulus on-line during a delay, even after exposure to distracting stimuli (Miller EK, Erickson CA & Desimone R, 1996). These neurons are thought to underlie the maintenance of internal representations (content) that are not available to the sensory organs anymore. Indeed, results from electrophysiological recordings performed on neurons in the primates PFC, show that there are neurons with sustained *delay specific activity* throughout the entire retention period (but not necessarily before and after this period) (Fuster JM & Alexander GE, 1971; Kubota & Niki 1971; Funahashi, S., Bruce, C. & Goldman-Rakic, PS., 1989; Goldman-Rakic PS., 1996; Hasegawa R, Sawaguchi T & Kubota K, 1998; Tsujimoto S & Sawaguchi T, 2004).

1.2.2 Working memory at the macro level

Brain activity studies in humans as well as in primates have shown that prefrontal areas are bilaterally active during performance of WM tasks (and that there also are parietal cortex and the basal ganglia activations) (in humans: D'Esposito M, Aguirre GK, Zarahn E, Ballard D, Shin RK & Lease J, 1998a; D'Esposito M, Postle BR & Rypma B, 2000a; Smith EE & Jonides J, 1998a; Lewis SJG, Dove A, Robbins TW, Barker RA & Owen, AM, 2004) (In animals: Goldman-Rakic, P. S, 1995; Inoue M, Mikami A, Ando I & Tsukada H, 2004). This sustained activity is thought to be the mechanism mediating WM functioning; either by maintaining stimuli specific information temporarily stored in the prefrontal neuronal network per se, or by driving networks with connections to posterior neuronal assemblies that store modality specific information. In humans delay specific activity is not necessarily restricted to maintenance of an earlier sensory stimulation, but can represent processing of a mental representation, for example an instruction of prospective action. Thus information held in WM is thought to be; either transiently *stored* in PFC, alternatively *controlled* from the PFC and parts of the parietal cortex (Goldman-

Rakic P, 1987). In the latter view, interactions between PFC and stimulus-specific sensory areas mediate WM.

My own opinion is in line with this interpretation. WM processes probably don't take place in one spot in the brain; i.e. the anatomical substrate that underlie WM whereto representations are copied and transiently buffered. But more reasonably, is carried out by interacting networks whose activity is regulated from the PFC. WM may be operating by top-down control, recurrently directing attention to relevant representations, which are (probably) stored in more posterior regions of the brain. (Desimone R & Duncan J, 1995; Miller EK & Cohen JD, 2001; Smith EE & Jonides J, 1999; Courtney, SM et al. 1998a; D'Esposito, M., Ballard D, Zarahn E & Aguirre GK, 2000b). How well these cortical areas are connected to and communicate with other areas in the brain that store relevant representations (i.e sensory areas) affects the effectiveness of WM. Given that top-down signals from PFC enhance internal representations of sensory stimuli in posterior parts of the brain, efferent signals from the PFC may have different functional implications, depending on which cortical region it communicates with. For example, sensory areas for perceptual processing of visual or auditory stimuli in the posterior cortex store different kinds of information, but both can be under the influence of top-down control from the PFC. This theory is supported by studies which show that prefrontal cooling remove neurons in more posterior areas the ability to retain stimuli in WM (Quintana & Fuster, 1993). Moreover others (Fuster JM, 1985; Chafee and Goldman-Rakic, PS., 2000) have found that deactivation of the lateral PFC cortex decrease the response of visual cortical neurons to a relevant stimulus. In order to be in the position to influence other areas of the brain, connections within and from the PFC are widespread, the PFC projects to many other areas in the cortex (Petrides M & Pandya DN, 1994; Ongur D & Price JL, 2000).

1.3 MULTIPLE DOMAIN OR MULTI-MODAL WORKING MEMORY?

Is WM one unitary system processing different kinds of information, or is WM a number of different systems specialized in processing different content as Patricia Goldman-Rakic has proposed? The most well known model, that of Baddeley and Hitch (1974), is somewhere in between. According to this model which stems from cognitive psychology, WM has a domain-specific organization with specialized sub-stores that are regulated by a third separate entity that operates as a central executive. The executive unit is thought to manage the allocation of attentional control to the slave systems, which stores short term representations of diverse content, either verbal or visual (see also § 1.4.3 *Working memory in attention, inhibition and executive control*).

1.3.1 Verbal working memory

According to the view of Baddeley and others verbal WM can be divided into a storage and a rehearsal component. By using imaging methods such as positron emission tomography (PET) or fMRI, or methods that interfere with neuronal activity such as transcranial magnetic stimulation (TMS)[1] while healthy subjects perform WM tasks, the *rehearsal component* of verbal WM has been located to frontal speech areas, i.e. Broca's area in the inferior frontal gyrus (Nixon P, Lazarova J, Hodinott-Hill I, Gough P & Passingham R, P 2004). The *storage component* is thought to be in a more posterior area in the parietal cortex (Paulesu E, Frith CD & Frackowiak RS, 1993; Awh E, Jonides J, Smith, EE, Schumacher EH, Koeppe RA & Katz S, 1996). The storage component is thought to hold verbal information for a few seconds, but without rehearsal managed from the frontal speech areas, the information would be lost due to decay (Baddeley, Thomson, & Buchanan, 1975). The duration in which the information can be held is thought to be prolonged by the use of *subvocal rehearsal*, i.e. repetitive covert articulation of the information held in the phonological store.

[1] TMS is applied by holding a coil that produces electromagnetic pulses over a part of the cortex. The pulses interfere with brain activity locally.

1.3.2 Non-verbal working memory

There is data from both animal and human studies on the neuronal substrate for non-verbal WM. Electrophysiological studies in primates have shown that there is position specific cells in the PFC which are activated selectively during spatial WM tasks (Goldman-Rakic PS, 1995; 1996; Tsujimoto & Sawaguchi, 2004). Functional imaging shows that the PFC is activated also in humans during performance of non-verbal WM tasks together with activations in the parietal cortex (Owen AM, Evans AC & Petrides M, 1996; Smith EE, Jonides J & Koeppe RA, 1996; Klingberg T, O'Sullivan BT & Roland PE, 1997). There are some indications on asymmetrical activation with relatively greater left hemispheric recruitment in verbal WM tasks and right hemispheric involvement in non-verbal WM (Smith EE, Jonides J & Koeppe RA, 1996). However, an increase in bilateral activation can be seen with increasing task demand, suggesting functional recruitment from the corresponding contra-lateral areas (Smith EE, Jonides J & Koeppe RA, 1996; Klingberg T, O'Sullivan BT & Roland PE, 1997).

Visuospatial information can, hypothetically be processed by an equivalent to the verbal rehearsal loop, i.e. through repetitive rehearsal of locations, mediated by covert rehearsal of eye-movements, this suggestion is supported by the activation in or close to the frontal eye-fields (FEF) during tasks of spatial WM (Courtney SM et al., 1998a; Awh E, Anllo-Vento L & Hillyard SA, 2000; see also Study I).

1.3.3 Supramodal working memory areas

Regardless of the type of WM task to be performed; there is a widely distributed WM network activated, including prefrontal and parietal regions (Klingberg T, 1998; Duncan J & Owen AM, 2000; Sylvester, CYC, Wager TD, Lacey SC, Hernandez L, Nichols TE, Smith EE & Jonides J, 2003). There is some support from neuro-imaging studies on the distribution of different WM networks. These networks though, are not entirely separated but partly overlapping. There are areas in frontal premotor cortex (Broca's area) predominantly activated during performance of verbal WM and a counterpart for visuo-spatial information is found in a fronto -parietal neuronal network. However the major parts of regional activation, evoked by performance of different WM tasks, are overlapping. The intersections are found in prefrontal and

parietal association areas, which implies that these areas mediate supra modal function (Klingberg T, Roland PE, & Kawashima, R. 1996) (see also §1.4.3.1).

1.3.4 Content or process-specific organization in the prefrontal cortex

Some functional imaging studies support a regional distinction between the processing of spatial and object information in WM (Belger A, Puce A, Krystal JH, Gore JC, Goldman-Rakic P. & McCarthy G, 1998; Courtney SM, Ungerleider LG, Keil K & Haxby JV, 1996; Sala JB, Rämä P & Courtney SM, 2003), whereas as others have suggested that these activation patterns are better accounted for by differences in the executive demands of the task (Petrides M, Alivisatos B, Evans AC & Meyer E, 1993). Others again (D'Esposito M et al., 1998a) has not found any evidence for a dorso-ventral subdivision of prefrontal cortex depending on the type of material held in WM. Those who advocate a process-specific organization suggest that that ventrolateral frontal cortex is more activated during the maintenance of information, while the dorsolateral frontal cortex is more active in manipulating information (Petrides M et al., 1993). The PFC in humans is involved in higher executive functions such as manipulation of information in WM but these areas do also show task related activity when only maintenance of a single item is required but memory load is high, such as during prolonged delay (Cohen J, 1997). Moreover, electrophysiological studies show that there are neurons in the prefrontal cortex of monkeys that are sensitive to both the object identity and spatial location of objects (Miller EK & Cohen J, 2001). These findings imply that the PFC is involved both during maintenance and processing of content in WM and supports the idea that different modalities of WM is managed by overlapping neuronal substrates.

1.4 WORKING MEMORY AT A FUNCTIONAL LEVEL AND ITS RELATION TO OTHER COGNITIVE CONSTRUCTS

1.4.1 Short term versus working memory

The concept of WM, earlier referred to as STM, has undergone some modification since it was introduced. STM was thought to have two functions: (1) storing material on-line for a few seconds, as when we rehearse a phone number until we dial it, and (2) providing a gateway to LTM (Atkinson R & Shiffrin R, 1968).

While cognitive scientists in the psychological tradition continue to consider the simple storage as one component in a multi level system, the theory of a gateway function has been discarded since there are patients impaired on STM tasks, but performing normally on LTM tasks (Shallice T & Warrington EK, 1970). Conversely, patients suffering from Korsakoff Syndrome perform normally on WM tests, but their LTM is poor. In modern cognitive neurosciences the term 'working memory' is most common and the concept of WM has been widened to include, not only maintenance of information, but higher cognitive functioning as reasoning and problem solving. If considering the storing part of WM as a memory for the short-term, this function relies on strategies such as rehearsal and chunking while WM is more complex and consists of both storing, manipulation and attention components (Engle RW, Kane JM & Tuholski SW, 1999). Moreover, the extent to which a task demands WM is determined by the extent to which it requires active maintenance of information that otherwise should be lost due to interference (Lustig C, May CP & Hasher L, 2001).

As there is no clear-cut distinction between STM and WM, there are no ''pure'' measures of either STM or WM (Cowan N, 1995; Engle RW, Kane JM & Tuholski SW, 1999). Conway et al (Conway ARA, Cowan N, Bunting MF, Therriault DJ & Minkoff SRB, 2002) has argued that the more a task forces the participant to engage in controlled effortful processing rather than automatized skills, the more the task tap WM capacity, and the less STM (Conway ARA, et al., 2002). Consistent with this, there is no objective measure that separates between STM and WM. It all depends on the individual's capacity; a STM task for an adult can be considered a WM task for a child. The latter is also applicable for individual differences in capacity within the same age-group (Engle RW, Kane JM & Tuholski SW, 1999).

1.4.2 Long term versus working memory

LTM and WM relies on different anatomical substrates and underlies diverse cognitive functions, thus these are easier to separate than the distinction between STM and WM. LTM is dependent on structures in the medial temporal lobe; hippocampus and enthorhinal cortex, which WM is not (Milner B, Squire LR & Kandel ER, 1998). Neural substrates underlying WM involves prefrontal and parietal areas. Some activation in prefrontal areas known to underlie WM is also present during performance of LTM tasks (Nyberg L, Marklund P, Persson J, Cabeza JR, Forkstam C, Petersson KM & Ingvar M, 2003; Ranganath C, Johnson MK & D'Esposito M, 2003), this can be due to that some tests of LTM contain features that demands WM. Time resolution and storage capacity also separates between the concepts of WM and LTM. The amount of information held on-line in WM is limited and lasts for seconds while there is no known capacity limit for amount and storage of information in LTM. Moreover, WM and LTM functioning, respectively, show different developmental trajectories. WM displays a continuous developmental trend from childhood (age 4-5 years) and does not peak until late adolescence (16-17 years). On the contrary, LTM functioning emerge adult-like after an age of about seven years (Gathercole SE, 1998).

Although WM and LTM are separable entities they are often used together. For example WM doesn't only maintain representations from the external world but also past representations of already known information stored in LTM. This information can be conceptualized as memory traces in LTM temporarily activated over threshold in WM (Fuster JM, 1995). WM capacity also influences the success of retrieval from LTM in tasks where the use of controlled and effortful search is needed. For example in tasks featuring parameters that tax temporal ordering of information, source memory and free recall (Squire LR, 1987).

1.4.3 Working memory in attention, inhibition and executive control

The concept of WM is closely related to some other cognitive constructs. These are attention, interference control and executive control. These are cognitive constructs close to but separable from WM, although sometimes overlapping with each other.

1.4.3.1 The central executive versus executive WM

According to Baddeley's WM model there are specialized sub-components that are regulated by a third separate entity operating as a central executive. The least defined part of Baddeleys model of WM is how the central executive carries out its functions and where in the brain it resides. To answer this, Baddeley proposed that the central executive could be identified by using a kind of subtraction technique; comparing brain activity when a subject performs one single task with that evoked when two different tasks are performed simultaneously, a so called *dual task*. Performance of dual tasks demand more effort than the sum of two single tasks performed separately. In order to carry out two tasks simultaneously, the requirement of a third resource, the central executive is suggested necessary. The central executive is thus not needed during performance of the single tasks separately, but becomes active in the management of dual tasks or otherwise intensified work load. Another explanation derived from research in the neurosciences agrees upon the hypothesis that when work load increases, as for example in dual tasks, more effort is required. But instead of supposing additional activation in any third supra-ordinate area, increased activity is proposed in the very same neuronal substrates that underlies performance of the single tasks respectively (Klingberg 1998). Brain imaging-studies on dual tasks using stimuli for different modalities (as verbal and visual) have showed that the areas activated during performance of single tasks are also activated during the performance of dual task (Adcock, AR; Constable, RT; Gore, TJC and Goldman-Rakic, PS., 2000). These findings suggest that executive processes requested as a function of increased work load, may be mediated by the same neuronal substrates that are engaged in performance of single tasks and not by any third area dedicated to executive functioning solely (Klingberg T, 1998; Bunge SA, Klingberg T, Jacobsen RB & Gabrieli JDE, 2000; Gruber O. & von Cramon D.Y, 2003; Adcock, AR; Constable, RT; Gore, TJC and Goldman-Rakic, PS., 2000). In this unitary view of WM, storage and control functions are thought to be carried out by overlapping neuronal networks. Data from brain imaging studies in humans (Sylvester, C-Y C., Wager, TD., Lacey, SC., Hernandez, L., Nichols, TE., Smith, EE. & Jonides, J., 2003) as well as in animals during performance of working memory tasks, support the latter view (Inoue M, Mikami A, Ando I, Tsukada H., 2004).

As the content in dual task stimuli can be from different domains, e.g. visual or verbal, this suggests that WM is a partly domain-free capability, independent of processing level or stage and much more general than suggested in the domain specific model (Engle RW, Cantor J & Carullo JJ, 1992). WM is for example related to higher cognitive functioning as reasoning and problem solving. An example is mental calculation where the subject has to temporarily store the outcomes of intermediary calculations and then to perform further computations on these temporary products (Richardson TE, Engle RW, Hasher L, Logie RH, Stoltzfus ER, Zacks RT, 1996). The term executive WM is thus more applicable than the term central executive.

1.4.3.2 WM and attention

WM is a prerequisite for the selection of relevant information to attend to and the filtering out of irrelevant information, functions that also can be described as c*ontrol of Attention* or *top-down attention* (Desimone & Duncan, 1995; Engle RW, Kane JM & Tuholski SW, 1999). On the contrary *bottom-up attention* is stimulus driven; unexpectedly occurring events in the external world tend to automatically attract our attention. This function is of high survival significance, since it alerts us about potential dangers. Bottom up attention is not voluntary controlled and does not require intentional effort to be activated. The *control of attention* model of WM place less emphasis on a storage role of PFC and instead emphasize its executive role in providing top-down control over more posterior cortical areas where the information is thought to be stored (Miller, E.K. and Cohen, J.D., 2001; Smith, E.E. and Jonides, J., 1998; Knight, R.T. and D'Esposito, M., 2003). Anatomically, visuospatial WM and visuospatial attention activate similar brain regions (LaBar K, Gitelman, DR; Parrish,TB; Mesulam, MM 1999 ; Pollmann and von Cramon, 2000). As top-down attention and eye movements partly activate the same anatomical areas in humans (Corbetta, M., Akbudak, E. et al., 1998) and as these areas also correspond anatomically to the neuronal substrates that underlies visuo-spatial WM (Awh E, Anllo-Vento L & Hillyard SA, 2000), this relations implies that visuo-spatial WM and top-down attention are overlapping functions.

1.4.3.3 WM and Interference control

WM capacity reflects the ability to maintain information in an active state and this is particularly important under conditions of interference. If inhibition is insufficient, more irrelevant information loads the WM system. Given limited resources, the system gets pre-occupied with irrelevant information and the capacity left for processing of task-relevant information is reduced. Negative priming is a phenomenon that explains this view. An example of negative priming is that it takes longer time to identify a specific object if it was used as a distracter in the previous trial. This may reflect the active inhibition of responses that are at risk to compete with the current target (Stoltzfus, Hasher, Zacks, 1993). Also de Fockert, Rees, Frith & Lavie (2001) has shown that WM is crucial for maintaining the prioritization of test-specific information and thereby reducing distractions from irrelevant stimuli. Another indication on the role of WM in the control over interference is the significantly improved performance on the Stroop test (a test that tax resolution of interference) after training of WM (see study 3, 4 and 6).

1.4.3.4 Working memory and general cognitive ability

WM is thought to underlie several cognitive abilities, including logical reasoning and problem-solving (Hulme & Roodenrys, 1995; Engle RW, Kane JM & Tuholski SW, 1999). The explanation of the central role of WM in different cognitive tasks such as reasoning and problem solving, could be that WM is involved in the regulation of activity in other (more posterior) regions in the brain (Petrides M & Pandya DN, 1994). During WM tasks information is kept on-line available for immediate access for other cognitive processes. This kind of active maintenance is essential for a variety of tasks such as language comprehension and problem-solving (Carpenter, P.A., Just MA & Shell P, 1990). Moreover, individual differences in WM capacity is a predictor of performance of a variety of cognitive abilities, including language comprehension, reasoning and computer-language learning (e.g., Daneman & Carpenter, 1980; Anderson JR, 1983; Kyllonen & Christal, 1990; Shute VJ, 1991; Kane MJ & Engle RW, 2003).

In a detailed task analysis of the Ravens matrices (a test for analytical reasoning intended to measure fluid intelligence) Carpenter, Just & Shell (1990) concluded that a mediator for success in solving the task was the discovery and maintenance of rules that regulate the variation among different factors in the problem. More difficult matrix problems typically involve more rules. Thus, in order to solve difficult matrix problems, the rule (or common denominator) must be discovered and kept online concurrently while searching the second rule and so on. Therefore, the ability to maintain goal-relevant information (i.e., rules) in the face of concurrent processing and distraction is essential for successful performance on Ravens progressive matrices. This may also be true translated to a behavioural level, for example in following verbal instructions. The individual has to be receptive for the information provided which often contains sequences of information, then maintain and be able to follow the instructions and execute the essential actions in a consecutive order.

Some researchers have argued that processing speed accounts for the relationship between WM capacity and fluid intelligence (Jensen, AR 1998; Kail R & Salthouse TA, 1994; Salthouse, TA, 1996; Fry and hale 1996). According to this argument, processing speed is a general characteristic which determines capacity because the processing of information (i.e. encoding, maintaining and responding) in WM takes time. The faster the rate of processing, the greater the amount of information that can be processed in one time unit. According to this hypothesis, the cause of above-average WM capacity may be generally higher processing speed. However we did not found support for this hypothesis in our own data, for a discussion see §3.1.2.3.2.

1.5 ON COGNITIVE DEVELOPMENT

Development during childhood and adolescence is characterized by maturation in a number of domains; better control of motor behaviour such as balance and coordination, and greater efficiency in cognition as for example language, perception and intellectual processing. A description which fits well, both with physical and psychological maturation, is the definition of development as the gradual growth an individual undergoes through a series of successive changes in their progression from lower to higher state of organization. Results from studies on performance on different cognitive tasks have showed that children gain higher capacity in a number

of areas as they grow older, such as enhancement in WM capacity and control of attention. In parallel with the WM development the child becomes more capable of inhibitory control and less distractible and impulsive. Cognitive and behavioural maturation is not a function of older age per se, but is consecutive to the morphological maturation of the nervous system. Developmental changes take place in chronologically and qualitatively different ways in various regions of the brain. The exact relationship between brain maturation and cognitive development is not explored in detail. Most of the data comes from autopsy studies, for example where the progress of myelinization throughout childhood and adolescence has been documented (Yakovlev & Lecours, 1967). It has been stated that these changes are regional and that the PFC is one of the last areas to mature (Flechsig, PE, 1920). The protracted maturation of the PFC might be a result of the late myelination of axons in this area (Klingberg, T., Vaidya, C. J., Gabrieli, J. D. E., Moseley, M. E., & Hedehus, M. 1999; Olesen, P., Nagy, Z., Westerberg, H., & Klingberg, T., 2003; Nagy Z, Westerberg H, Klingberg T., *in press*). Both in phylogeny as well as in ontogeny, the PFC has a protracted development. Since the PFC is involved in higher executive functions, such as WM, it is of particular interest in developmental studies. However, it is not until the last 15 years with the introduction of modern functional brain imaging techniques that the neural bases of cognitive development has become accessible for in vivo observation, also in healthy children. The combination of fMRI and diffusion tensor imaging (DTI) provides the exclusive opportunity to document, both function and connectivity within the developing central nervous system (CNS). One has to be aware, though, that it is the correlations between the development of anatomical substrates and the associated development of cognitive functions we can discover with the current technique, but we can not verify the causal relationships.

1.6 ON COGNITIVE TRAINING

Cognitive training is a broad concept within which various types of interventions have different objectives. The goal can either be to *retrain* a cognitive function or to *compensate* for the deficits by the use of alternative strategies. Cognitive training also includes psychotherapeutic interventions promoting insight

and acceptance of the new life situation one may experience after a brain injury. The retraining approach aims to improving the impaired function by training. This kind of intervention often focuses on cognitive components related to the impaired ability, whether it is perception, attention or as in the current thesis, WM. However, the two approaches are not mutually exclusionary but can be applied in parallel, and possibly even strengthen each other.

1.6.1.1 Cognitive training in older age and after brain injury

It has been proven hard to influence LTM functioning by the use of retraining interventions. For example practice in memorizing word lists or numerical series (Derwinger A, Neely AS, Persson M, Hill RD & Bäckman L, 2003) have turned out to improve learning lists or number series specifically, but failed to generalize to other memory functions. When assumed that the impaired cognitive function cannot be improved by training, the treatment strategy instead is to provide the patient with techniques that by compensating ameliorates the symptoms. Examples of this approach include the implementation of meta-cognitive strategies for more efficient memory encoding and retrieval, for example mnemonics as the method of loci (Hill DR., Bäckman L., Stigsdotter, Neely A., 2000). The compensatory approach, which also includes technical equipment that facilitates planning and reminds about events, such as handheld microcomputers (palm pilots), is the most commonly used and is thought to be the most efficient way to support patients to live their life autonomously (Wilson B, Emslie H, Quirk K, Evans J, 2001).

The retraining approach has had some success in improving basic cognitive skills such as attention and speed of cognitive processing, at least when reviewing the literature on cognitive rehabilitation in participants with acquired brain injury. Studies have showed improvements on the trained task itself and in some cases also gains in other outcome measures (Cicerone KD, Dahlberg C, Kalmar K, et al. 2000). But the major draw back of the cognitive retraining approach is that transfer of the treatment effects, in respect of improvements of similar abilities, or transfers of skills to milieus outside the treatment setting, have not been evident to any great extent. Transfer effects have been particularly hard to demonstrate from the trained task to abstract cognitive functions such as reasoning and problem solving and to cognitive functioning in daily living. Another problem is to control for the effect of

spontaneous recovery which is a substantial factor in explaining improvement during the first weeks and months after a brain injury. Attention training has been evaluated in the *acute* phase after brain injury in four controlled studies (Novack, Caldwell, Duke & Berquist, 1996; Schottke, 1997; Sturm, Willmes, Orgass & Hartje 1997; Ponsford & Kinsella, 1998). The researchers were able to distinguish treatment effects in one group from spontaneous recovery in a control group on some aspects of the trained tasks but there was no generalisation to measures of attention in daily life.

To our knowledge there are seven studies that have evaluated the efficacy of attention training in the *post acute* phase after brain injury (Sohlberg MM & Mateer CA 1987; Strache 1987; Niemann H, Ruff RM, Baser CA. 1990; Gray JM, Robertson I, Pentland B, Anderson S. 1992; Park NW, Proulx GB, Towers WM 1999; Sohlberg MM, McLaughlin KA, Pavese A, Heidrich A & Posner MI 2000 and Cicerone KD, 2002), most of them focusing on traumatic brain injury (TBI) but three included subjects with stroke as well (Sohlberg et al 1987; Strache 1987 and Gray et al 1992). Of these, four studies (Sohlberg et al 1987; Strache 1987; Park et al 1999; Sohlberg MM, 2000 and Cicerone KD, 2002) have showed some positive results but these studies were either non-randomized (Strache, 1987 and Cicerone KD, 2002) or in lack of a control group (Sohlberg et al 1987 and Sohlberg et al 2000), which makes it difficult to interpret the results. Furthermore the studies by Sohlberg 1987 and Cicerone 2002 included only four participants each in the treatment condition. There are also one controlled but non-randomized study (Park et al 1999) that found no significant treatments effects at all. Two studies (Strache 1987and Gray 1992) reported that the treatment was computerized. And two reported that computer based attention training were included although in combination with other interventions (Sohlberg et al 1987 and Niemann et al 1990). The Attention Process Training programme (APT) was used in three of the studies (Sohlberg et al 1987, Park et al 1999 and Sohlberg et al 2000). APT is a hierarchically organized method directed at retraining of attention in a step-wise manner from; sustained, selective to alternating and finally divided attention. Only two earlier randomized, controlled studies have had positive findings (Niemann et al 1990 and Gray et al 1992). Gray et al reported that after training, the treatment group showed improvement as compared to the control group on measures of attention, but when pre-morbid intelligence score and time since injury were controlled for, the treatment effect was no longer significant. But at the follow-up six months after training, there was a significant difference between the groups on measures of attention and WM. In the Niemann et al study

(1990) the treatment group improved significantly more than an alternative treatment group on several measures of the attention and WM tasks. Only one study reported measuring the functional outcome of training in daily life, Sohlberg, MM et al (2000) who found improvements in attention and memory, they also found significant improvements on the PASAT task. There are considerable differences in a number of factors across the studies. For example in characteristics of the participants included, such as age, type of injury and time since injury, but also in parameters concerning content and duration of training-intervention, as well as in outcome measures. However among the post acute treatment studies, seven (including our own) have included the PASAT test which makes, at least crude, comparisons between treatment effects across studies possible. Slightly different versions of the PASAT test were used, regarding parameters as inter stimuli interval (ISI) and total number of stimuli. To compare between studies we calculated the effect sizes (ES) on the raw scores from the PASAT test from each study (see table 1). The ES was calculated by subtracting the difference between pre- and post- training scores in the control group from the difference between pre and post training scores in the treatment group and dividing the sum by the pooled variance from both groups (delta treatment group - delta control group)/pooled SD).

Study	**ES**
Niemann et al 1990	-.16
Gray et al 1992	.31
Park et al 1999	.26
Sohlberg et al 2000	.12
Cicerone, 2002	.90
Westerberg et al, *submitted*	.79
Mean	***.33***

Table 1. Comparison between ES on PASAT test scores from the post acute training studies (Sohlberg et al 1987 did not report raw scores on the PASAT test why calculation of ES was impossible).

What we can conclude from the comparisons of ES's on the PASAT test between studies is: (1) that cognitive training show positive results and (b) that the two studies with the highest ES (Cicerone KD, 2002 and Westerberg H, Jacobaeus H, Hirvikoski

T, Clevberger, P, Östensson M-L, Bartfai A & Klingberg T, *Submitted*) included training of WM. Notably, in the study with negative ES (Niemann et al 1990) the "comparison" treatment, which the attention training method were compared to, was the computerized training software; the *Einstein Memory Trainer*. This programme includes memorizing by visualization and association, teaching techniques of recall as method of loci, as well as coding and sequencing of information. The declaration of programme content suggests that the programme operates on aspects of both LTM and WM. This can be the reason to why there was a *negative* ES on the PASAT results in the Niemann et al study; the comparison method was just as effective as the treatment method they primarily intended to evaluate. The difference in raw-score was 5.9 in the attention training group and 7.5 in the memory training group. This can be compared to a difference of 6.6 raw-scores in the treatment group in our study (Westerberg H, Jacobaeus H et al, *Submitted*), which was a significant improvement compared to the results in the passive control group (0.6).

1.6.1.2 Computerized Cognitive Training in ADHD

Deficits in WM is hypothesised to underlie the symptoms of Attention Deficit Hyperactivity Disorder (ADHD) (Barkley RA, 1997; Castellanos FX & Tannock R, 2002; Rapport et al., 2000; Westerberg et al., in press). Thus it is reasonable to direct a systematic treatment intervention aimed at improving WM in ADHD, and examine the effects, not only on WM, but also on other symptoms (see §1.6.3). Furthermore computerized cognitive training after brain injury has been proven to have some positive effects (Cicerone KD, 2001) (see also §1.6.1.1), among the best studies were those including demands of cognitive control processes as manipulation of information in WM (Cicerone KD, 2001).

The methodological advantages of computerized training over traditional cognitive training are that the programme content easily can be individualized and that the game-like design as well as immediate feed-back is found appealing, especially to children. Moreover an infinite number of trials with randomized stimuli configurations can be produced effortlessly and all information on performance such as accuracy, reaction time, time on task are automatically recorded and can be used to monitor compliance and to provide adequate feed-back (Gianotsus R, 1992). However, there have been a very limited number of studies reported on the efficacy

of computerized cognitive training in subjects with ADHD (Kotwal DB, Burns WJ & Montgomery DD, 1996; Slate SE, Meyer TL, Burns WJ, Montgomery DD, 1998; Tinnius TP & Tinnius KA 2002). Two are, although with promising results, only case studies, but one of them (Tinnius TP & Tinnius KA 2000) is a controlled trial including 15 participants. In this study about 20 sessions (30-45 minutes each) of computerized cognitive training on STM, attention and problem solving were combined with neruo-feedback, implemented by Electro-Encephalography (EEG) technique in thirteen adults with ADHD. Significant treatment effects as compared to controls (N=15) were found on computerized measures of attention as well as on self rating scales on attention and academic functioning.

1.6.1.3 Treatment studies in ADHD

Pharmacological and psychosocial treatments are the most explored methods in ADHD treatment. The most commonly administrated pharmaceutical is methylphenidate which has effects on symptoms of impulsivity and hyperactivity and also on cognitive functioning and attention. Behavioural therapy (operant conditioning) has showed results in better self regulation of behaviour, but not on cognitive functioning per se. Pharmacological treatments are the most thoroughly investigated and also the most effective treatment known, to date. The Multimodal Treatment Study of Children with ADHD (the MTA study, sponsored by the American National Institute of Mental Health) included 579 children, pooled over four conditions. Although they found significant treatment effects in the group receiving intensive behavioural therapy compared to the control group, the effect was even larger in the medication treated group (Swanson, J. M., Kraemer, H. C., Hinshaw, S. P., Arnold, L. E., Conners, C. K., et al., 2001). In a review Farmer et al (Farmer EMZ, Compton SN, Burns BJ, Robertson E, 2002) went through the evidence based pharmacological and psychosocial treatments for ADHD. They included articles with interventions for 6–12-year-old children conducted between 1985 and 2000, were ADHD was the primary diagnosis and the article focused on treatment outcomes. To be included, studies had to be controlled and/or randomized treatment outcome studies. They found six articles providing outcomes of psychosocial treatments for ADHD with varying approaches from cognitive–behavioural therapy, parent training, EEG biofeedback training to special diet and social skills training (Fehlings, D. L., Roberts, W., Humphries, T., & Dawe, G., 1991;

Horn, W. F., Ialongo, N. S., Pascoe, J. M., Greenberg, G., Packard, T., et al. 1991; Linden, M., Habib, T., & Radojevic, V., 1996; Long, N., Rickert, V. I., & Ashcraft, E. W., 1993; Pfiffner, L. J., & McBurnett, K., 1997; Schmidt, M. H., Mocks, P., Lay, B., Eisert, H. G., Fojkar, R., et al., 1997). Studies involving EEG biofeedback, parent training, and cognitive behavioural therapy showed positive changes on some of the rating scales when comparing results to a wait-list control group. There were no evidence of generalization of treatment effects beyond the treatment setting and at follow-up the differences between groups was no longer evident. However there is one more study fulfilling the criteria in the Farmer et al review (2002), that they failed to include. Kimberly Kerns and colleagues (Kerns KA, Eso K, Thomson J, 1999) evaluated the effect a children version of the APT program by Sohlberg & Mateer (1987) in 14 children diagnosed with ADHD. After intervention children in the treatment group improved significantly as compared to a control group on non-trained tests of attention and cognitive performance. However, rating scales from parents and teachers on symptoms related to ADHD did not differ significantly.

1.6.2 Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder (ADHD) is present in between 3-5 % of the school-aged population. ADHD is diagnosed according to certain characteristics described in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994), known as DSM-IV, (see table 2). Developmentally inappropriate behaviour characterizes children with ADHD, including significant problems in the areas of attention, impulsivity, and hyperactivity. These symptoms should have been present early, typically before the age of seven. Moreover, the symptoms shall be persisting, and last at least six months. All children appear to be inattentive, impulsive, and overly active sometimes, but in the case of ADHD these behaviours are pervasive. Children with ADHD also often experience problems in the areas of social skills and self esteem; these problems may be secondary to the core symptoms of ADHD. Since the ADHD diagnosis is based on description of symptoms it is particularly important to check for differential diagnosis, since similar behaviours can co-occur or be confused with Oppositional Defiant Disorder, Conduct Disorder or even with reactions due to psychological stress.

Table 2.

DSM IV Criteria of ADHD

A. Either (1) or (2)

(1). Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
Inattention
(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities, (b) often has difficulty sustaining attention in tasks or play activities, (c) often does not seem to listen when spoken to directly, (d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions), (e) often has difficulty organising tasks and activities, (f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework), (g) often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books, or tools), (h) is often easily distracted by extraneous stimuli, (i) is often forgetful in daily activities

(2) Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.

Hyperactivity
(a) often fidgets with hands or feet or squirms in seat, (b) often leaves seat in classroom or in other situations in which remaining seated is expected, (c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness), (d) often has difficulty playing or engaging in leisure activities quietly, (e) is often "on the go" or often acts as if "driven by a motor", (f) often talks excessively

Impulsivity
(g) often blurts out answers before questions have been completed, (h) often has difficulty awaiting turn
(i) often interrupts or intrudes on others (e.g. butts into conversations or games),

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years. **C**. Some impairment from the symptoms is present in two or more settings (e.g. at school and at home). **D**. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning. **E**. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder)
(ADHD Combined Type, if both A1 and A2 for at least 6 months)

1.6.3 Working Memory deficits and ADHD

In the search of the underlying causes of ADHD one crucial step is to identify measurable characteristics that may serve as mediators between genetics and manifest behaviour. Converging data from studies using neuroimaging and pharmacological methods (Giedd, Blumenthal, Molloy, & Castellanos, 2001; Castellanos FX, Sharp WS, Gottesman RF et al. 2003; Durston, S, Tottenham, NT, Thomas KM et al, 2003;

Bedard AC, Martinussen R, Ickowicz A, Tannock R, 2004; Mehta MA, Goodyer IM & Sahakian BJ, 2004) implicate that the causes of ADHD is found; neuro-chemically in subtle deviations in certain neurotransmitters (dopamine) and anatomically in alterations within the fronto-striatal system. These coincides with the neural substrates that underlie WM, and thus the altered functioning of these substrates is compatible with WM deficits in ADHD, suggesting WM as the proximal cognitive construct, i.e. the *endophenotype*, mediating between neurobiology and behaviour in ADHD (Castellanos FX & Tannock R, 2002) (for further discussion see §4.1.1.5.1). There also are earlier reports on the significance of WM deficits in ADHD. In Barkley's theory of ADHD (Barkley, RA, 1997) WM deficits are central, although he emphasises dysfunction in inhibition as the core deficit hampering the development of executive functioning. Furthermore in a review by Rapport et al. (Rapport, M. D., Chung, K. M., Shore, G., Denney, C. B., & Isaacs, P., 2000), the authors concluded that a common factor for the most sensitive tests in discriminating between children with and without ADHD, was the involvement of a WM component.

Deficits in WM are manifested at a behavioural level as impairment in executive functioning, such as planning and organization of goal-directed behaviour. These factors interfere with functioning in all major life activities; on leisure activities and in social interactions. Needless to say, shortcomings in these areas affect these children's self-esteem negatively. The difficulties children with ADHD experience in academic activities are consistent with the importance of WM in scholastic abilities such as reading, arithmetic and problem solving (Mariani, M. A. & Barkley, R. A., 1997). Thus, the rationale behind an intervention of WM training in ADHD is obvious; given that WM is impaired in ADHD it is logical to direct treatment interventions at these symptoms, and furthermore to determine whether this treatment also improves functioning at a cognitive level as well as ameliorates the behavioural symptoms in ADHD.

1.7 HYPOTHESIS

To find and evaluate a psychometric test that is valid and reliable in measuring VSWM capacity as well as is sensitive in detecting WM deficits. This is reported in Study II.

In Study I, we investigate the neural correlates underlying developmental change in WM capacity.

Given that the VSWM test is sensitive for the cognitive deficits in children with ADHD, the next question would be if it is possible to improve WM capacity. And if so; can the training effect generalize to other cognitive tasks and areas of behaviour? If it is possible to improve WM capacity in children with WM deficits, is it also possible to treat other patient-groups with significant WM deficits? These research questions are tested in Study III, IV and V, by the implementation of a special designed computerized training programme for systematic training of WM.

If it is possible to detect training induced change in behaviour, what then are the neuronal correlates underlying this change? This is explored in Study VI.

2 METHODS

2.1.1 Psychometrics -tests of WM and executive functions

For the assessment of development of VSWM in children in study I and II, we adapted a test with documented sensitivity for cognitive development during childhood (Fry AF & Hale S, 1996; Hale S, Bronik MD & Fry AF, 1997). We used similar task parameters but implemented in another software environment. The task was programmed and presented using E-prime-software (Psychology software tools inc. Pittsburgh, USA). We then performed a preliminary confirmation study in 17 children in different ages with our own version of the task, which showed that our version of the test was as sensitive as the original test (Westerberg, H., 2000). The VSWM test requires the participants to remember sequences of spatial information. The more spatial locations remembered, the greater the WM capacity is estimated to be.

2.1.1.1 Parameters in the VSWM test

Filled circles (memory stimuli) were presented one at a time in a four-by-four grid on the computer screen. In study I, II and III responses were made by pointing (using the index finger on a touch screen) in an empty grid on the touch screen in the same locations as the memory stimuli. The response was to be made after all stimuli in each trial were presented. WM load increased after every second trial, starting at two and ranging to nine circles. The test terminated when the participant failed to accomplish both trials at a certain level. WM capacity for each participant was determined by cumulatively adding the numbers of circles (items) indicated, from all trials up to the highest level reached. Grid representation at display was 22 cm x 22 cm. The participants were positioned so that the face was about 40 cm from the display. The same stimuli sequences were administrated to all participants. The display time was 2250 ms, and the ISI was 750 ms.

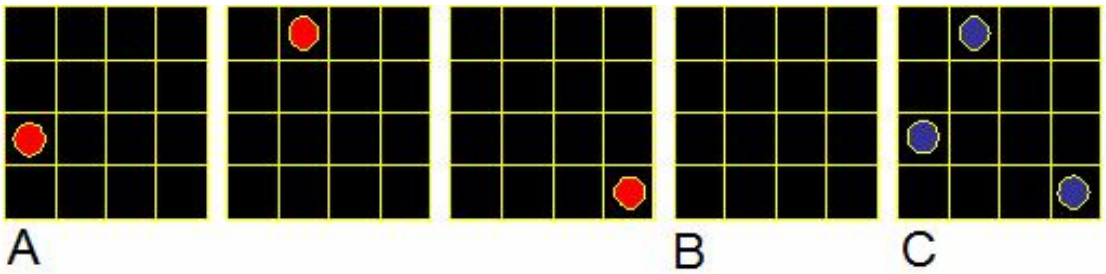

Figure 1. A. Stimuli is presented one by one B. a delay period follows and C. finally the participant responds by indicating the locations in which the stimuli appeared.

2.1.1.2 Discussion on the VSWM test

The VSWM test contains a number of sub-components: (1) to perceive a sequence of items presented in different locations, (2) maintaining information on the interrelations of the spatial localisations and their serial order online during a delay as well as (3) maintaining the prioritisation of test-specific information and thereby resisting distractions from irrelevant stimuli, i. e. inhibit interference from items earlier presented (both intra-and inter trial information) (4) execute the correct motor responses when indicating the target locations in the response phase. WM includes and is related to all these subprocesses (see also §1.4.3), however, it is difficult to know exactly which of these components that constitutes the bottle neck of performance on the VSWM test. Research by Rowe et al (Rowe JB, et al., 2000) on the sub-components of a VSWM task indicates that the maintenance and response selection phases are central to this type of WM task but that they are associated with activity in different parts of the PFC.

In summary the particular VSWM test we have utilized has the following features (1) a visuo-spatial component; (2) more than one stimulus to maintain; (3) unique sequencing of stimuli-order in each trial; (4) short delays during which the stimuli should be maintained and (5) multiple response alternatives.

2.1.1.3 Reliability and validity of the VSWM test

We checked the test-retest reliability for the VSWM test by correlating the test scores from two different test points with five weeks in between, in 18 individuals (11 adults and 7 children). There was no intervention in between. The Paerson product moment correlation coefficient (r) for the VSWM test (N=18) was .77

A valid test measures what it is supposed to measure. For example, a test for WM measures this ability rather than the verbal ability necessary to understand complicated sentences. The Validity of VSWM was assessed by correlating the results on the VSWM with those from a criterion measure known to be valid, the span-board from WAIS-NI. The concurrent validity was .67 (N=18). The discriminant validity was assessed by correlating the standardized scores on a test for LTM, word list learning with the scores on the VSWM test, the result was -0.12 in N=11, thus confirming that these two tests measures different cognitive abilities.

2.1.1.4 Test parameters in the choice reaction time test (CRT)

This test was used in study II. The task was to press a button as quickly as possible when a warning signal (grey circle) switches to target (yellow circle) (see figure 2). This was first performed with one circle and one button at the far left side of the screen and the response was to be made with the left index finger, this was followed by the same procedure on the right screen side, and with the right index finger. Subsequently two horizontal circles were presented and two buttons were used, one for each finger. One of the two circles turned from grey to yellow in a pseudo randomised order, and the child had to make a decision between pressing the button with the left or right finger corresponding to the yellow circle and respond as quickly as possible.

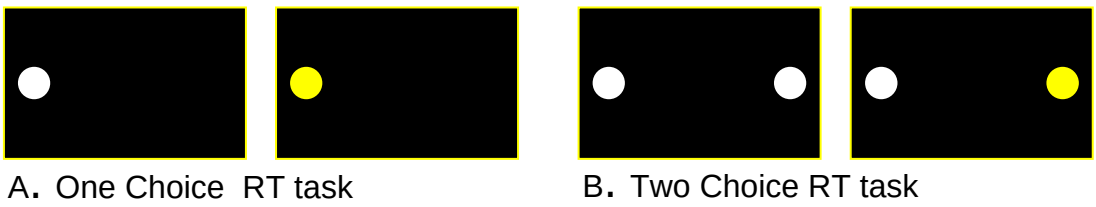

Figure 2. A. Basic psycho-motor speed; the participant pressed a button as fast as possible when the single stimulus lit up. B. In the two choice version there were two warning probes but only one of them lit up, in randomized order and time intervals. The participant indicated the target one by pressing a button on the corresponding side.

The delta value was defined as the increase in median reaction time in the two-choice version compared to the one-choice version. A measure of the constancy of attention can be obtained by calculating the standard deviation for each child. The stimulus onset asynchrony of the warning cue was randomised between 1000 and 4000 ms. Maximum response time allowed was 2000 ms. The inter-trial-interval was 2000 ms. The distance between the participant's face and the monitor was about 70 cm for standardisation of the visual angle of display. Fifteen trials were administrated on each side in the one-choice condition and 30 pseudo random trials (15 left and 15 right) in the two-choice condition.

2.1.1.5 Test parameters in the scanner version of the VSWM test

Children's version (Study I)

The children were asked to remember the location of red filled circles (cues) that were presented sequentially in a 4 x 4 grid. After a 1500-ms delay, a probe-circle appeared and the child pressed a button if the unfilled circle was in the same location as any of the filled circles had been earlier (see figure 3). Two versions of this task were given during scanning: one with three filled circles to remember and one with five, but the presentation time was held constant (7000 ms).

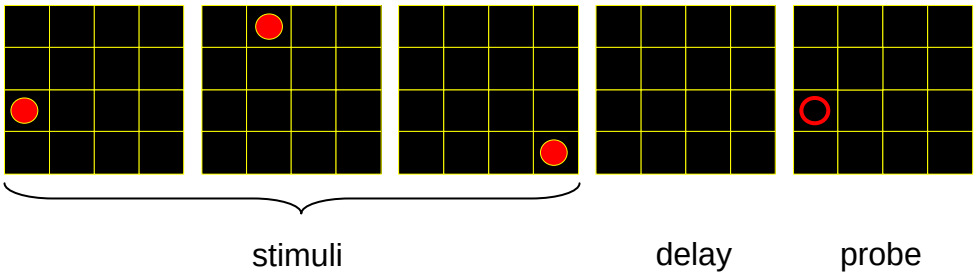

Figure 3. The VSWM test administrated in the scanner

Adult version (Study IV, experiment 1)

The participants were asked to remember the location of red filled circles that were presented sequentially in a 4 x 4 grid on a display. Each cue was presented for 900 ms (ISI 500 ms). The participant's had to remember the location as well as the order in which the cues were presented. After a delay (1000 ms) a response phase of 2000 ms followed. The inter-trial interval (ITI) was 1000 ms. During the response phase an unfilled probe circle with a number in it (1-5) appeared. The participant had to judge

whether the probe was in the same location as any of the five cues and, if so, whether the number within the probe corresponded to the serial position of that cue. If both location and number in the series matched, the participant pressed a button with their index finger to indicate “yes”, otherwise they pressed another button, using the middle finger to indicate “no”.

Control task for both children (Study I) and adults (study VI, experiment 1)

In the control condition, the participants watched five green filled circles that were presented one-by-one in each of the four corners (top-left, top-right, bottom-left, or bottom-right and top-left again). After a 1500-msec delay, a green unfilled circle (probe) appeared in the middle of the grid and the subjects responded by pressing the button with their index finger each time the probe appeared. In the adult version there was also a number inside the probe.

Adult version (Study VI, experiment 2)

WM task performed during scan in Experiment 2. Five (low load) or seven (high load) red, filled circles (cues) were presented sequentially in a four-by-four grid. Each cue was presented for 900 ms, with 500 ms ISI. The last cue in the sequence was followed by a blank grid and a text line indicating the start of the response phase which lasted 12000 ms. During this time the subject should indicate the location and order of the presented cues by moving a cursor on a computer screen by the use of an optic track-ball. The ITI was 5000 ms after low load trials and 2200 ms after high load and control trials.

Control task (Study VI, experiment 2)

Seven green filled circles were presented sequentially in the two top rows. Presentation times for the cues were identical to that in the WM task. The circles stayed on the grid when the text line appeared and the task was to “unlit” them by clicking at them one by one, by means of the optic track-ball.

2.1.1.6 Neuropsychological outcome measures

We have used a number of tests measuring WM, attention and executive functioning as outcome measures in the treatment studies, although all the tests were not used in all studies. The tests are listed in the following section: (a) Span-board from the Wechsler Adult Intelligence Scale-Revised NI (WAIS R-NI) (Kaplan, E., Fein, D., Morris, R. & Delis, D., 1991), was used as a measurement of visuo-spatial WM. Ten wooden blocks are positioned on a brick in a fixed semi-structured order. The participants were asked to reproduce a sequence of pointing at different blocks using the index finger in their best hand. The same sequence is never given twice, and the number of stimuli items is increased every second trial, starting with two. Firstly the participants were asked to reproduce the stimuli presentations in the same order as they were given. When the participant fails twice to reproduce a sequence at a given level the task ends. Then the same procedure is repeated but the participants are asked to reproduce the sequence in the opposite order to the original sequence. The mean raw score from all trials was used in the statistical analysis; (b) the Stroop interference test, Dodrills format (Dodrill, C.B., 1978) reflects the ability to inhibit an over-learned response. In this task 100 words describing the colours blue, green, red and yellow are randomly listed, ten words per row. All words are printed in a colour incongruent with the word, e.g. the word “green” is printed in yellow ink. The subjects were asked to name the colour of the ink for each word as correct and as fast as they could; (c) Digit-span from WAIS R (Wechsler, D. WAIS-R Manual, 1981), a measure of verbal WM. The administration is similar to that of the span-board test; but the stimuli are digits read aloud instead of visuo-spatial locations. The participant shall reproduce increasing numbers of digits heard, first in the same order as presented and in the second part of the task, subjects are asked to reproduce the digits in reverse order; (d) Raven’s progressive matrices is a test intended to measure non-verbal reasoning ability. Increasingly complex items are given were the participant, by inductive reasoning, shall figure out the underlying principle and choose from a series of alternatives what piece is left out from a matrix. Ravens coloured (1995)-, Ravens standard (1995)- and Ravens advanced (1990) progressive matrices were used in the children with ADHD-, adults with stroke- and adult fMRI- training studies respectively. In children all 36 items were administrated but in both adult studies eighteen items were administrated, odd numbers before and even numbers after the training period (e) Paced Auditory Serial Addition Test (PASAT) (Gronwall DMA.,

1977) was given as a non-trained test for WM and attention. A continuous stream of 60 digits is read out from a pre-recorded CD. The ISI is 2.4 seconds. The task is to add the two latest digits heard and tell the sum aloud. As the reading goes on the participant must continuously update the two latest digits heard and add them (f) A Word list recall test (Claeson L-E, Esbjörnsson E, Carté B-M, Wahlbin M, 1971) was used as a measure of learning and LTM. A fixed sequence of ten words is presented until the participant has learned it (maximum ten presentations). After 30 minutes the participants were asked to recall as many as possible of the learned words. Word list delayed recall was evaluated by asking the participants to recall as many as possible of the ten words memorized 30 minutes earlier (g) RUFF 2&7 (Ruff RM, Niemann H, Allen CC, Farrow CE, Wylie T., 1992) is a serial cancellation test intended to measure attention. Digits are displayed by three rows per segment, on a paper sheet. The participants are asked to cross out all digits “2” and “7” they can find as fast as possible until the test leader says “Next”, then the participants are instructed to stop working with the actual segment and start all over with a new one. The test leader says “Next” every 15 seconds. The context in the segment where the digits “2” and “7” shall be crossed out differs and can be either other digits or letters. The original test consists of 20 segments, but in this study we only used the first ten. The tests were administrated in the same order as quoted above (h) OPTAx System (OPTAx Systems, Burlington, MA). The OPTAx System is combined measurement of accomplishment at a Continuous performance test (for 15 minutes) and concurrently of hyperactivity, by the objective quantifying of head movements (Teicher MH, Ito Y, Glod CA, Barber NI., 1996). An infrared motion analysis system recorded the movements of a small reflective ball (25mm) attached to the back of the head of the participant. A movement was defined to begin when the marker moved 1.0 mm or more from its most recent resting location. In the continuous performance task the participants were asked to respond to a target (50% of stimuli were targets) and withhold response to non-targets. ISI was 2.0 s.

2.1.1.7 Ratingscales

In the second study on WM training in children with ADHD (study IV), the ADHD symptoms were scored by both parents and teachers using the 18-item rating scale from DSM-IV (American Psychiatric Association, 1994) and by using the Conners’ Rating Scale (revised, short version) (Conners, CK., 2001). Symptoms were scored

by assigning a severity estimate for each symptom on a 4-point scale, from 0 (not at all) to 3 (very much). In Study VI, the self rating scale *Cognitive Failure Questionnaire* (CFQ) (Broadbent DE, Cooper PF, FitzGerald P, Parkes KR., 1982) was used to score symptoms of cognitive failures, as for example attention lapses and memory problems in daily living. The CFQ is a frequency scale and includes 25 items, each item was scored from 0 (never) to 4 (very often). The score is the total for all of the items (maximum is 100).

2.1.2 Training method

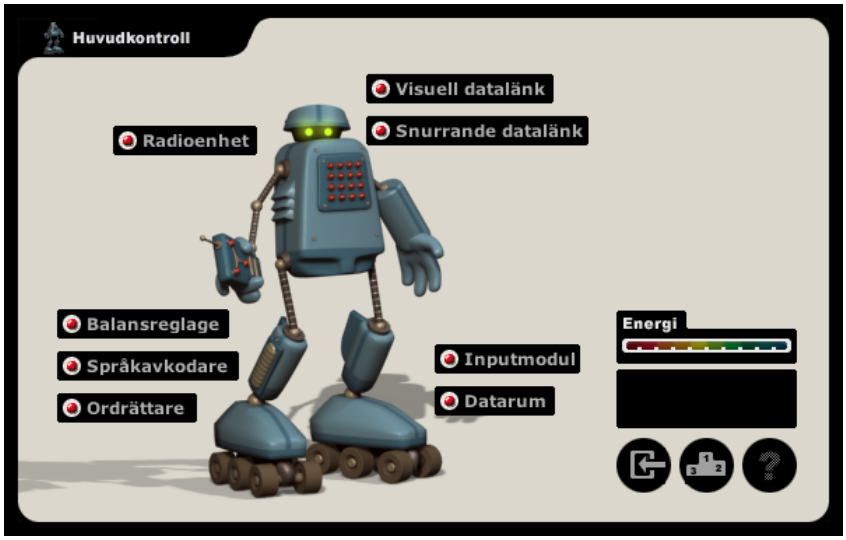

Figure 4. Main menu of the training software.

In study III we evaluated the efficacy of a prototype of the WM training programme. The study rendered promising results but the method had to be developed further for use outside the research setting. Improvements in the method, the software as well as the therapy management, were needed. Such a project require financing and by support from Karolinska Innovations AB the founders (Jonas Beckeman, Torkel Klingberg, David Skoglund and Helena Westerberg) were able to establish a research company (Cogmed Cognitive Medical Systems AB) dedicated to developing the method with the goal to bring the method to clinical use.

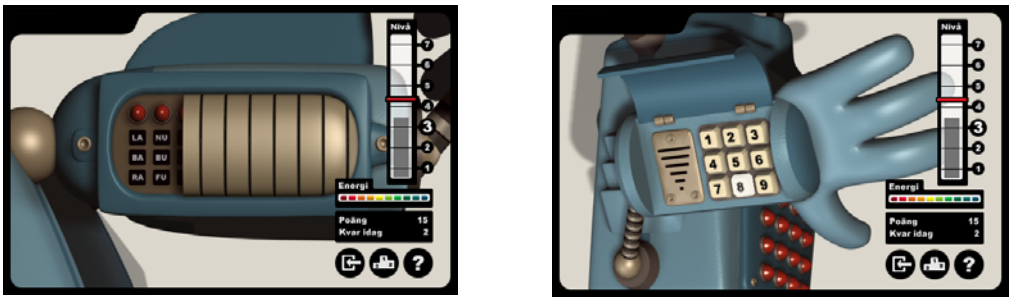

Figure 5. Verbal WM tasks: A. Sequencing of pseudo words B. Digit span backwards

The training method is implemented by a computerized programme (*RoboMemo*© from Cogmed Cognitive Medical Systems AB, Stockholm, Sweden) which is performed at home on a personal computer (PC). The software contains a battery of different visuo-spatial and verbal tasks focusing on WM. To enhance motivation the tasks are incorporated in a setting of a modern pedagogical computer game for children. Examples of the tasks are; sequences of pseudo words (figure 5a), digits presented are to be reproduced backwards (figure 5b) or visuo-spatial target locations that shall be repeated. The tasks are offered a few at a time, but to provide variation with the intention to boost motivation, the tasks are changeable. New more difficult tasks (for example with moving targets or with representation in 3D, see figure 6), replace the old ones throughout the training period.

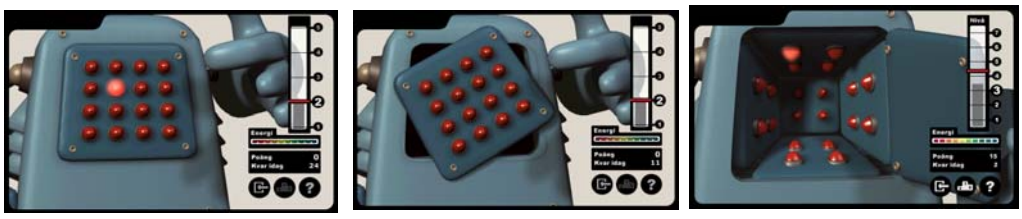

Figure 6. Versions of the visuo-spatial WM task, with different difficulty-levels.

A treatment plan specifies the number of trials to be performed during the training period. In sum there are 90 trials (which equals at least 30 minutes of training) per day for five days per week, during five weeks. Depending on the results on the different WM tasks the ratio of trials on different tasks can be individualized at any point of time during the training period. Moreover, to optimize the training effect, the difficulty of each task is titrated close to the capacity limit of each participant and continuously adjusts as a function of the individual's performance. The practice of adaptively varying the intensity- and difficulty parameters has proven effective in earlier training studies intended to increase sensory functioning (Tallal, P., Miller,

S.L., Bedi, G., Byma, G., Wang, X., et al, 1996; Temple E, Deutsch GK, Poldrack RA, Miller SL, Tallal P. et al, 2003).

The comparison “low-dose” training programme used in study III and IV was identical to the treatment condition except that the difficulty of the WM tasks remained on the same low level (two-three items) instead of being continuously adapted to fit each child’s WM capacity.

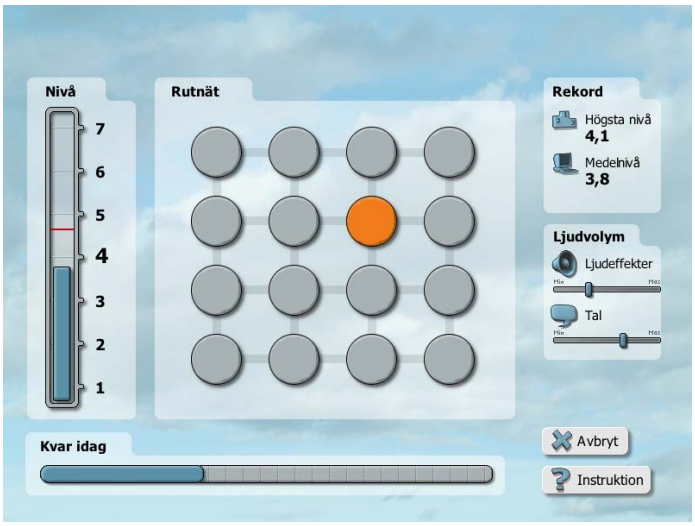

Figure 7. One of the visuo-spatial WM tasks from the training software designed for WM training in adults.

The training software includes immediate reinforcement implemented by scores and verbal feedback on performance. In addition to the computerized training, the treatment method also provides supervision and frequent feed-back over the telephone by a therapist who monitors compliance (frequency and duration of training) and training progress. Feedback and advice on motivation strategies was given weekly by a certified psychologist in study IV and V.

To obtain an adequate basis for this evaluation, the participants are asked to report data on their training results via the internet. This is easily implemented since the software automatically extracts a log-file which the participant, by clicking an icon on their desktop, transfers to a server at the hospital. In the log file responses to every trial is logged to a file on the computer. Every second day, an adult who was responsible for the child’s training, uploaded the file with the training results to the server at the hospital, via the internet. This was done also in the comparison group in order to verify compliance. Details on the specific version of the software used is provided in the discussion of each training study (§ 3.1.3, 3.1.4, 3.1.5, 3.1.6).

2.1.3 Functional brain imaging, linking biology to behaviour

2.1.3.1 Magnetic resonance imaging

In the MR-scanner, raw data on anatomy is acquired in the form of signals of radio frequency which are send out by excited hydrogen atoms at different gradients in the magnetic field (Ogawa S, Lee TM, Kay AR, Tank DW. (1990). The technique utilizes the relaxation properties of the magnetically excited hydrogen nuclei. Hydrogen atomic nuclei occur in all parts of the body and the MR-technique is sensitive to the relative density of these nuclei in different tissues. First, the spins of the nuclei in the tissue are aligned in a strong magnetic field. Then, radio frequency pulses are applied in a plane perpendicular to the magnetic field to cause some of the hydrogen nuclei to change alignment. After this, the radio frequency is turned off and the nuclei go back to their original configuration (relaxation). During relaxation radio frequency energy is released and then recorded by coils surrounding the head of the participant. By the use of the inverse Fourier transform (a mathematical method of analysis) the frequency data can be converted to information that can be translated into images (Lauterbur PC., 1986). One of the advantages of an MRI scan is that, according to current medical knowledge, it is harmless for humans. The technique only utilizes strong magnetic fields and non-ionizing radiation in the radio frequency range.

2.1.3.2 Blood oxygen level-dependent effect (BOLD)

There is a relation between neuronal activity and the vascular response. Increased neural activity causes an increased cerebral metabolism which in turns demands oxygen. Oxygen is transported coupled to haemoglobin in the erythrocytes. When the consumption of oxygen is increased, which occurs when the metabolism increases due to neural activity, the requirement for oxygen is reassured by an increase in blood flow. The increase in blood flow happens to be larger than the oxygen extraction. Thus the vascular system overcompensates the demand for oxygen and there is actually an increase in the amount of oxygenated relative to deoxygenated haemoglobin. The haemoglobin acts as an endogenous contrast for local changes in brain activity since the haemoglobin have paramagnetic characteristics. (It is the iron bounded to haemoglobin that has paramagnetic characteristics). In its oxygenated state haemoglobin gives a signal increase related to local neural activity. Energy is

released and recorded by coils surrounding the head of the participant in the same manner as when acquiring the anatomical images. Earlier the hypothesis was that the local increase in blood flow was related to the firing of energy-consuming action potentials from the large pyramidal neurons. Recent hypothesis is that instead it is the post potential synaptic activity that consumes most energy and thus is reflected by increases in blood flow (Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. (2001). The contrast between brain activity-pattern at the time point when the task, for example a WM test is given is compared with the activity at the time point when a control task is performed. The control task is designed to control for non specific activations due to motor activity and sensory stimulation that co-occurs with the actual task, WM in this case. The control task is often constituted of the same task parameters as the task of interest, minus the active component. (For task parameters used in Study 1 and 6 see. §2.1.1.5) We used a 1.5 T GE Signa scanner to accumulate the MRI and fMRI data. T1-weighted spin echo images, FOV = 220 x 220 mm, 256 x 256 grid, were acquired for anatomical images and normalized to Talairach space using a template from the Montreal Neurological Institute. The functional data were T2*-weighted, gradient echo, spiral echo-planar images acquired in the same position as the anatomical images.

2.1.3.3 Analysis of fMRI data

Scanning was performed in a blocked design alternating between WM and control tasks. Changes in blood oxygen level dependent (BOLD) response was analysed using Statistical Parametric Mapping (SPM99) (Welcome Department of Cognitive Neurology, London, UK) using the general linear model, either fixed effects or random effects. For the statistical analysis we often used a fixed effect analysis where we calculated a subtraction image representing the WM condition minus the control condition activity for each subject. The subtraction images were then entered into a second-level random effect analysis in which WM capacity (measured outside the scanner for children, and meanwhile scanning in the adults) was used as the variable. A regression analysis was performed on the subtraction images from the first-level analysis to find areas where BOLD response values correlated with WM capacity. Significance was determined as a function of the size of the clusters of voxels with values above a predefined threshold. Motion during scanning was estimated by six parameters (three translations, three rotations) which were used to realign the

functional images to the first image in the series, and later used as confounds in the statistical analysis.

2.1.3.4 Ethical issues in functional magnetic resonance imaging

The MR technique is not dangerous in itself; there is no need for invasive contrasts or radiation. However the examination does invade on integrity and can be experienced uncomfortable because of the extraordinary apparatus and restrictions during the procedure. It is especially important to ensure that pediatric subjects are treated respectfully and ethically, as they do not have the same ability as an adult to imagine how the participation in a prospective situation may be experienced. It is important to put effort into preparing the participants, especially children, before they participate in an fMRI examination. This will ensure that any fear associated with the procedure is minimized and also increase willingness to cooperate. We approached this by using a protocol in children that familiarized them with the procedures they were going to participate in, ensuring us that they had comprehension of the situation and the rationale, for example, for wearing earphones and staying as still as possible without talking for 30 minutes. When siblings participated it was helpful to use the older one as role model, i.e. the big brother or sister went through the procedure first, while the younger sibling had the opportunity to watch. They could follow how the other child entered into the magnet, were shown a movie, participated in the WM task and came out and got rewarded for participation, for example by receiving movie tickets (Hinton VJ, 2002).

3 RESULTS AND DISCUSSION

3.1.1 Study I – Increased Brain Activity in Frontal and Parietal Cortex Underlies the Development of Visuospatial Working Memory Capacity during Childhood

3.1.1.1 Introduction

Modern non-invasive brain imaging technique opens the opportunity to study brain-behaviour correlates that take place during development of the nervous system, in vivo in children. Until now the understanding of at least some aspects of cognitive development associated with human brain growth has come from autopsy studies where the relation between development of different brain regions and the functional development has been based on *post hoc* correlations. In study I, fMRI was used to measure brain activity in 14 children between 9 and 18 years of age while they performed a VSWM task and a baseline task controlling for unspecific matters as perceptual and motor activity. The research question concerned if it would be possible to observe changes in neuronal activity associated with the increase in WM capacity, known to take place from childhood to adulthood (Fry & Hale 1996; Zald DH & Iacono WG, 1998).

3.1.1.2 Results

During performance of the WM task, the older children showed higher activation of cortex in the superior frontal and intra-parietal cortex than the younger children did. A second analysis found that WM capacity was significantly correlated with brain activity in the same regions. Thus the development of these areas may underlie the development of spatial WM during childhood. For details on method and results see study I.

3.1.1.3 Discussion

In this study we found that as a function of age as well as of capacity, there was higher activation in the superior frontal and intraparietal cortices during performance of the VSWM test. The development of these areas may underlie the

development of VSWM, among other higher cognitive functions, during childhood. These areas are also known to be involved in the control of attention and spatial WM. A later study on the development of WM confirmed the significance of activity increases in these areas (Kwon, Reiss, & Menon, 2002). Moreover, it has also been shown that increased brain activity in the superior frontal cortex during childhood is correlated with improved performance on the Stroop task, a visual task requiring control of attention and response inhibition (Adleman et al., 2002). Taken together these results suggest that the development of the functionality in these areas might play an important role in cognitive development during childhood.

There are some uncertainties in the interpretation of data from small sample sizes, when additionally considering the heterogeneity of background variables as age and sex across these fourteen participants. It is a small sample to estimate cross-sectional developmental changes for an age span of ten years. There are risks of misinterpretation, and it is indeed difficult to make valid assumptions about any particular of these age groups. However we did not intend to make estimations of individual age groups, but of a developmental *trend* in brain activity across age groups. Moreover, the findings from this study were replicated in a consecutive study where we extended this sample by recruiting nine more children (in total N=23) Olesen, Nagy, Westerberg, & Klingberg, 2003.

3.1.1.4 Methodological issues on fMRI in children

Brain imaging is a complicated project and especially in children with still developing nervous systems there are some technical and statistical concerns. One is if the changes in brain size occurring during development are at risk to interact with the imaging data. The total *brain size* does not increase significantly after the age of 10-12 years (Kretschmann HJ, Kammradt G, Krauthausen I, Sauer B, Wingert F, 1986; Reiss, Abrams, Singer, Ross, & Denckla, 1996; Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL, 1999). In our studies the children participating were between 8 and 18 years old. To rule this possible confound out, we performed a correlation with age and data on certain coordinates (the linear scaling factor in the x, y, and z directions) from the anatomical normalization parameters in each individual. Consistent with earlier reports, no significant correlation between age and brain size was found in this sample. Moreover, does the BOLD response differ as a function of age which would be at risk

to interact with the functional imaging data? To exclude lower signal-to-noise ratio in the images from younger subjects, a ‘‘control-subtraction’’ was done. Since there were more visual stimuli in the control task than in the low load WM task (see §2.1.1.5), a subtraction of brain activity in the low load task from the activity in the control task would indicate such an effect in visual cortex. When brain activity during the low load task was subtracted from the control task, a large, significant activation in the visual cortex showed up. However, no interaction was found between activity in this area and age (p = .98,). This lack of interaction between visually induced activity and age confirmed that the interactions between WM-induced activity and age were real and not due to a generally lower signal-to-noise ratio in the younger children. How about movement artefacts? Subject movement in the scanner is always at risk to bias the data. In children this could be a systematic confound, with younger children moving to a greater extent and thereby inter individual rates of movement would interfere with task specific activity. To check for this, in the statistical analyzes on functional brain activity, six parameters describing head movement during scanning were included as confounds. This is a standard procedure, but in children the removal of signal correlated with head motion could potentially in itself introduce differences in signal detection corresponding to age (Josephs & Henson, 1999). To evaluate the effect of removing motion-correlated signals, we also correlated between motion and task-onset. There was no significant correlation between age and movement on the behavioural task demonstrating that the removal of signals correlated with head motion did not introduce any age-related bias. It is difficult to design the neuropsychological tasks so that the different age groups perform at the same level during scanning. This is crucial since increases in capacity on the neuropsychological task (VSWM in this case) affects tasks performance. Older children are more efficient in responding and spend less time on task than younger children. When performance during scanning varies inter individually, these differences interfere with age-related task specific differences in brain activity per se.

We approached this by keeping the WM load at a low level in the scanner, thus all children could manage the task. This intentionally created ceiling effect minimized the individual differences in performance during scanning. The “testing to the limits” to detect differences in WM capacity was done outside the scanner, were all subjects started at the same low level and then continued with stepwise increasing difficulty levels every second trial. The WM-related brain activity was then analyzed to find

correlations between brain activity and age, as well as between brain activity and WM capacity, by the use of the test data obtained outside the scanner.

3.1.1.5 Possible mechanisms sub-serving developmental change

What are the mechanisms behind the association between increase in brain activity and increase in cognitive capacity? Is it solely genetically programmed changes in the brain or is it experience with cognitive tasks that stimulate brain growth and indirectly cause the developmental changes seen in children's cognitive abilities?

Even if the total brain volume is constant there is a dynamic interplay of simultaneously occurring progressive events as myelination and regressive events as pruning, in which different brain regions follow different time courses. Structural changes in the brain which occur during development can be expected to correlate with location and amount of regional brain activation during the performance of different cognitive tasks. Learning also causes changes in the nervous system throughout development, for example in connectivity; in the competition that occurs during development, experience related activity is the mechanism through which some synapses are selected and others are pruned (Greenough WT, Black JE, Wallace CS (1987); Greenough WT and Bailey CH (1988). Although there are several maturational processes that coincide in time with the increase in WM capacity, one of them, myelination is of particular interest because the inferior parietal cortex, where we found an interaction between activity and age, is among the last brain regions to myelinate (Yakovlev & Lecours, 1967; Flechsig PE., 1920). Moreover there are now new brain-imaging techniques as DTI to measure this maturation. The combination of fMRI and DTI provides the possibility to document, both function and connectivity within the developing brain. To further investigate the anatomical foundations underlying cognitive development we also performed DTI in this particular sample of subjects (Nagy Z, Westerberg H, Klingberg T, *in press*). DTI is a recent application in the field of MRI. It allows the observation of molecular diffusion in tissues *in vivo*. With this technique one can indirectly map the organization and integrity of white matter in the brain. We found that development of cognitive abilities during the later part of childhood is correlated with maturation of white matter. The improvement of WM was associated with white matter integrity mainly in the left frontal lobe. Furthermore, we also performed a combined analysis of DTI and fMRI data that revealed that the white matter integrity in the superior frontal lobe is correlated with

brain activity in the superior frontal sulcus and intraparietal cortex in children (Olesen, Nagy, Westerberg, & Klingberg, 2003).

3.1.2 Study II - Visuo-spatial working memory span: a sensitive measure of cognitive deficits in children with ADHD

3.1.2.1 Introduction

In this study we investigated if the VSWM test would be sensitive enough to differentiate between children with and without ADHD we used a VSWM test that has a documented sensitivity for developmental changes in WM capacity (Fry and Hale, 1996; Hale, Bronik, & Fry, 1997; Westerberg H, 2000; Klingberg et al 2002), but that has not been used previously in ADHD research. Diagnostics and research in ADHD is based on descriptions of the patient's behaviour which only express the symptoms but not the causes. In the search of the underlying causes of ADHD one crucial step is to identify measurable characteristics, endophenotypes, that may serve as mediators between genetics and manifest behaviour. A main candidate among these is deficits in WM (Barkley, RA, 1997; Rapport et al. 2000; Castellanos FX & Tannock R, 2002). The rationale for choosing the VSWM test was that it measures WM capacity, a cognitive construct that is logically linked to the hypothesised patophysiology of ADHD, i.e. deficiency in fronto-striatal and dopaminergic circuits. The VSWM test requires the participants to remember sequences of spatial information. The more spatial locations remembered, the greater the WM span is said to be and this in turn is an estimate of WM capacity.

3.1.2.2 Results

In experiment 1 (a pilotstudy), the sensitivity of the VSWM test and a choice reaction time test (CRT) to discriminate between groups with and without ADHD was evaluated. This was done by comparing them to two commonly used tests in ADHD-research; the Continuous Performance Test (CPT) and a test for impulse-control, the Go/no-go test administrated in the same sample of children. The groups differed

significantly in performance on the VSWM test (*P<.01*) and CRT (*P<.05*) but not on the CPT (*P>.1*) or Go/no-go test *(P>.1*). The WM test turned out to be the most sensitive test in differentiating between the groups in this sample of children (see figure 8)

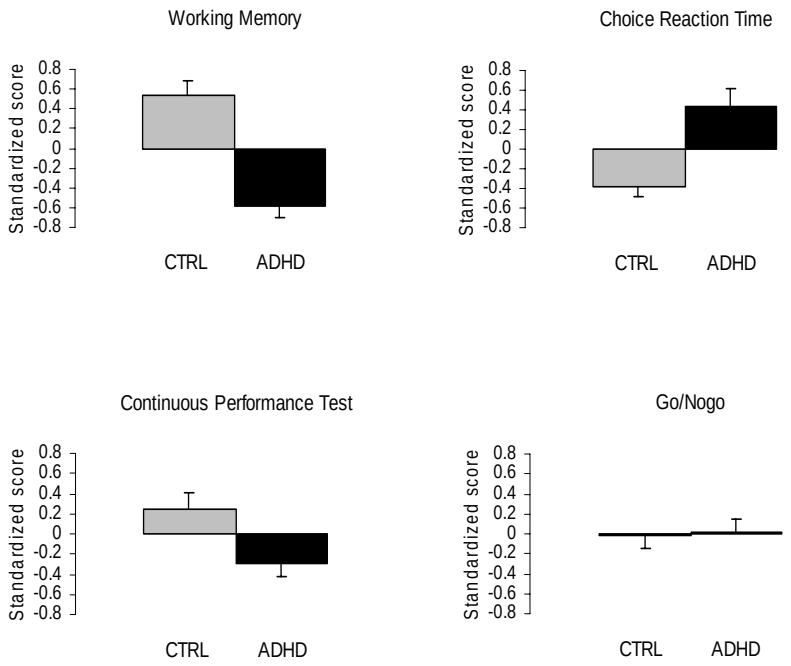

Figure 8. Comparisons of group differences in the four tasks experiment 1. The figure shows standardised scores after correcting for age.

The results from the VSWM and CRT tests were later replicated in a consecutive experiment in a larger sample of children (80 boys; 27 boys with ADHD and 53 controls, mean age 11.4 years). Significant differences between groups were found, on the VSWM test (*P<.01*) and on the CRT (*P<.01*). The ES of the VSWM test was 1.34. There was a significant age-by-group interaction on the VSWM test, with larger group differences for the older children (*P <.05*).

3.1.2.3 Discussion

WM deficits have been suggested to constitute a core deficit in ADHD. In this study we investigated and found that the VSWM test, used to track developmental improvement in study I, also was sensitive in detecting difference in cognitive performance between children with and without ADHD.

3.1.2.3.1 Age and group interaction

The memory load in this VSWM test, proceeded from two items per trial and upwards in ascending order, the maximum of items that could be reached was nine (see § 2.1.1.1). The total number of correctly indicated locations in all trials on all levels was taken as our measurement of the individuals WM capacity (maximum 88). This procedure which resulted in significant interactions between age and group with the differences between children with and without ADHD being larger at older ages needs further commenting. One factor is that despite the sensitivity of the VSWM test in discriminating between older children with and without ADHD, it may be a too crude *measurement* in detecting differences in younger children. This can be due to the feature of non-linearity in the difficulty increase between levels in the WM test. I.e. it might be easier to go from managing six to seven items, than from two to three items; the relative increase in load is 14% in the former and 33% in the latter example. Another factor influencing the large interaction between age and group could be that also the cumulative *scoring method* (Engle RW, Tuholski SW, Laughlin JE, Conway ARA, 1999) used in this study, puts a higher weight on difference between higher levels. I.e. when counting the cumulative score on all items from all levels reached, there is a bias towards steeper steps in the higher levels which exaggerates the discrepancies seen in the groups of older children. For example the difference between level 3-4 is 8 items (2 x 4) but the difference between level 5-6 is 12 items (2 x 6). Therefore we did a control analysis were we used the more traditional scoring method used by Hale, Bronik, & Fry (1997), were WM span was calculated at a level of load basis. If the final correct trial consisted of two correctly recalled series, the span was determined to be the number of items in these series. If the final correct trial included only one correctly recalled series, the span was determined to be the number of items in the series minus 0.5. For example, success at both trials at level four, only at one trial at level five and none at the level six would give a score of 4.5. By using this scoring method there was still a significant difference between the groups (P= 0.0004), but not a significant age by group interaction (P= 0.08) and the ES was lower; .88 (compared to 1.34 in the items procedure). This ES is close to that found by other groups using similar test paradigms for example Mariani and Barkley (1997) who found an ES of .89 and Barnett (2001) who found an ES of 1.06. However, when correlating the scores from

the analysis on *Level* with the ones from *Item* there was a .95 correlation which suggests that the measures are reasonably coherent.

3.1.2.3.2 Alternative interpretations on outcome

The explanation to the weaker results found in other studies utilizing WM tests in children with ADHD can be that these tests partly depended on episodic memory or only used low memory loads. Moreover there can be differences in how the diagnosis is set, in our study only boys with ADHD combined type and with no co-morbidity participated. This gives that the SD in this group is probably lower than in a more heterogeneous sample and a low SD affects the ES in a positive manner. Besides differences in test paradigms and scoring procedures one can speculate in other explanations, for example at younger ages there seems to be no group differences in the VSWM test scores. If this reflects the children's "true" WM capacity either children with ADHD don't have any WM deficits when younger but an earlier "silent" deficiency shows up in the school ages. Or they fail to participate in school by some other reason than WM deficits and thereby get less exposure to endogenously WM demanding tasks, as arithmetic and reading and thus don't get enough training to develop their WM capacity at an age appropriate level.

We certainly intended to measure WM capacity with the VSWM test, but there could also be alternative explanations since there can be other factors that unintentionally are mediated by the VSWM test. For example it is hard to control for the fact that the development of other cognitive functions than WM doesn't influence task performance, for example language which possibly influences the use of language based cognitive strategies. The VSWM is visually-guided and so are the responses from the participant, so probably the information to be held in WM is not mediated by verbal strategies. Also the concurrent validity of .67 with the span-board test from WAIS-R-NI (discussed in §2.1.1.3), which is attributed to measure visuo-spatial WM, strengthens this notion.

Latency and variability in responding in reaction time tasks have been suggested to differentiate between children with and without ADHD. This could possibly be related to WM in that choice reaction time (CRT) tasks measure speed of processing, which in turn have been hypothesised to determine WM capacity (Kail & Salthouse TA, 1994; Fry & Hale 1996; Jensen AR, 1998). According to this view, processing speed is the core concept which determines capacity of processing in WM

given that encoding, maintaining and response of information is performed in a cyclic manner (rehearsal loops) which each take some amount of time. Thus, the faster the processing is, the greater the amount of information that can be processed per time unit. In this view, speed of processing would be more fundamental, and tests such as the CRT would be more sensitive than the VSWM test to cognitive development, as well as in discriminating between groups with and without cognitive deficits. To further study this question, we also included a CRT test in the present study to see if the results on this test correlate with those from the VSWM test, and to see if the CRT test was even more sensitive than the VSWM test. The correlation between the CRT and VSWM tests in the present study was .40 and the WM test turned out to be the most sensitive test in differentiating between the groups. Thus we found no support for the CRT test as being equal to, or a more fundamental construct than WM.

Another interpretation can be made if considering interference as the core difficulty in ADHD. Vulnerability to interference may determine WM span scores, thus implicating inhibition as an important determinant of WM capacity (May, Hasher, and Kane (1999). May et al. presented subjects with different versions of reading and digit span task. Some memory sets proceeded from small sets of two items upward to large sets of six items, in “ascending” order. Others were presented in a “descending” order from large to small sets. The logic was that so called proactive interference may accumulate across memory sets. Thus affecting performance at the ascending span tasks more, because the higher levels with five or six items are attempted after completion of a number of earlier trials. On the contrary, the descending versions of the WM span task, interference will have less impact because trials at higher levels will be attempted before the easier ones, and thus the receptiveness of interference will be low. We did not control for this order of level effect in the present study.

Conclusion

Our results show that the VSWM test is a sensitive measure of cognitive deficits in ADHD and supports the hypothesis that a deficit in VSWM is a central component for the symptoms in ADHD. Once a central deficit is identified it should logically be the focus of treatment interventions, both pharmacologically but also for cognitive intervention (see study III and IV).

3.1.3 Study III-Training of Working Memory in Children with ADHD

3.1.3.1 Introduction

Research on the neurobiological correlates for ADHD indicates subtle deviations in the neurotransmitter-system (e.g. dopamine) and in some brain areas (i.e. striato-frontal). These coincide with the chemical and neuronal substrates that underlie WM functioning. These relations suggest WM as the proximal cognitive construct (i.e. the *endophenotype*), mediating between neurobiology and behaviour in ADHD. Logically, treatment interventions at the cognitive level should thus be directed at WM. In the present study, we used a new training method to investigate if it was possible to ameliorate these deficits in a group of 14 children with ADHD. In this study we applied a double blind approach so that neither the testing psychologist, nor the children or their parents were aware of which condition the child was pseudo-randomized to; treatment or low-dose treatment. The training program includes intense training of a number of WM tasks and the difficulty level is continuously adapted as a function of the individual's performance (see § 2.1.2). The version of the training software used in this study was a prototype containing only three different WM tasks and a choice RT task. There was (a) A visuo-spatial grid task similar to the VSWM test, i.e a four-by-four grid is displayed were the participant is instructed to watch a number of lamps lighting up and then reproduce the same sequence. (b) A Backwards digit-span task. A keyboard with numbers was displayed and then digits were read aloud. The child then responded by indicating the same numbers but in reversed order, by moving the cursor on the screen to the right digits and click on them (with the data-mouse). (c) A Letter-span task. Letters were read aloud one at a time. The child had to remember the identity and order of the letters. A row of lamps was then visible and a flashing lamp cued the subject as to which letter that should be reported back, e.g. if lamp no 3 was lit, the subject should report the third letter that they previously had heard. (d) Choice reaction-time task. This task was not a WM tasks but a mixture of a reaction-time task and a go/no-go task. This was included based on the results from our laboratory indicating that this type of task is sensitive for the cognitive deficits in ADHD (see study II). The children performed 30 trials on each task at least five days a week, for five weeks. The low-dose treatment constituted of the same type of tasks as in the real treatment but the difficulty level

remained at a low level. The aim of using this low-dose version as comparison treatment was to control for non-specific treatment effects that could occur as a function of being involved in a study. It's not earlier investigated if WM can be improved by training and if the training effect could generalize to other cognitive tasks and areas of behaviour.

3.1.3.2 Results

The training effect was evaluated by means of a neuropsychological test battery containing different tasks of executive functions. These were the trained WM tasks, the span-board test, the Stroop test and the Ravens progressive matrices. In addition we also applied the Optax test, a test measuring hyperactivity by quantifying the number of head movements during performance of a 15 minutes long vigilance test. All statistical analyses were on test-retest differences between groups. Training significantly enhanced performance on the trained WM tasks ($P = 0.0006$). Moreover, the training significantly improved performance on the non-trained executive tasks, not considered as WM tasks; the Span-board test ($P = 0.001$), Raven's Progressive Matrices ($P = 0.001$) and Stroop accuracy ($P = 0.02$). There was also significantly less hyperactivity as measured by the Optax system ($P = 0.00008$)

3.1.3.3 Discussion

After establishing that the VSWM test was sensitive enough to discriminate between high and low capacity performers inter individually (study II), we assumed that the test would also be sensitive in detecting changes in intra individual performance as a function of a training intervention. Significantly enhanced performance on the trained WM tasks were indeed found, but more importantly, the training significantly improved performance on a non-trained WM task and on the complex reasoning task. In addition, motor activity - as measured by the number of head movements during a computerized test – was significantly reduced in the treatment group.

To be able to interpret the results of intervention studies, treatments that are equated with the actual treatment in all ways, except those thought to be the essential treatment component, is required (Munakata, Y., Casey, B.J., & Diamond, A, *in press*). The present study is one of the few placebo controlled treatment studies in the field of cognitive training. Some earlier studies have compared different

interventions (Niemann et al 1990; Gray et al 1992; Tinnius & Tinnius 2000) but most have only compared pre and post training scores in the same sample.

WM has been seen as a stable intra individual trait, so the generalization of improvement from the training task to other non-trained task of WM, as span-board and digit-span is exciting and raises a number of question on the nature of WM and what this improvement can bring on to other areas of cognition. Some of these issues were scrutinized in this study. There were transfer effects to other executive tasks as the Stroop and the Raven test, which are not considered as WM tasks. One common denominator among the tests; VSWM, Stroop and Raven is that they all are known to rely on the PFC. The improvement on the Raven test and the Stroop test is evidence for that the training effect generalized to non-practiced tasks, since the training contained only WM tasks. These transfer effects give valuable clues on how different cognitive constructs may interact with each other. The improvement in reasoning ability can be explained by the fact that the results on tests for complex reasoning as the Raven's test correlates highly with performance on WM tests. Performance in the Stroop task is thought to be determined by two factors, goal maintenance and competition resolution, which both in turn depends on WM capacity (Kane, MJ & Engle, RW (2003). These relationships can explain the transfer from WM training to tasks as the Stroop and the Ravens matrices.

The decline in symptoms of motor hyperactivity after training of WM may be surprising. However there are links among these functions, for example in the basal ganglia which sub-serve initiation of both motor and cognitive behaviour. Fine motor skills as coordination mature in parallel with cognitive functions, neither reaching full maturity until late adolescence, this suggests that interrelations between neuronal systems for motor and cognitive processing may be, to some extent, overlapping (Diamond, A., 2000). However, the results on significant decreases in hyperactivity as measures by the Optax-system were not confirmed in the subsequent study (see Study IV).

A second experiment within this paper showed that similar training-induced improvements on cognitive tasks are also possible in young adults without ADHD, however their results are discussed in study 6 experiment 1. Taken together, these experiments show that WM capacity can be increased by training in children with WM deficits as well as in healthy adults who also could improve their WM capacity, although they started from a higher bas line. To conclude, these were

promising results which made us enthusiastic in performing further studies on training of WM in a larger sample.

3.1.4 Study IV - Computerized Training of Working Memory in Children with Attention- Deficit/Hyperactivity Disorder – a Controlled, Randomized, Double-blind, Trial

3.1.4.1 Introduction

In this study we investigated if it was possible to replicate the results on treatment effects from study III, *Training of Working Memory in Children with ADHD* in a larger sample, and at different clinical sites. We used the same outcome measures, Span-board, Digit span, Ravens matrices, Stroop and Optax, and in addition we administrated rating scales to parent and teachers.

Shortcoming of the first training study was the low number of subjects. Moreover we didn't provide any feedback on performance during training; we did no follow-up-testing to investigate the long-term effects of training; and the assessment was only administrated on one site, our own clinic. We did investigate the effect of training on different WM tests and possible transfer effects to other cognitive tasks, but we didn't assess outcome in the symptomatology of ADHD at a behavioural level, by means of rating scales. The present study was therefore conducted at four clinical sites evaluating the effects of WM training in a randomized, double-blind, controlled design. The training intervention includes intense training of a number of WM tasks and the difficulty level is continuously adapted as a function of the individual's performance (see § 2.1.2). The version of the training software used in this study included the WM task described in §3.1.3.1, and in addition three new tasks intended to train WM were included; (a) Sequences of the segments in a pseudo word were read aloud, responses were made by choosing the one correct segment out of three possible in columns, that in turn were sequentially ordered, until the whole pseudo-word was reproduced. (b). Match or miss-match of the segments between two pseudo-words read aloud, response were made by moving a cursor on the computer screen and indicate the miss-matching segments. (c). A rotating version of the visuo-spatial grid task. After the sequence of locations was presented, the grid rotated 90° clockwise and the child had to reproduce the right sequence in its (new) current locations. The choice RT task was not implemented in this study since we after

analysis of the training data from study III could conclude that this task did not contribute to the treatment effects. Feedback and advice on motivation strategies were given once a week both in the treatment and in the low-dose condition by the same certified psychologist, Maria Andersson. A neuro-psychological test battery was applied before and after the training period of five weeks, and also three months later. At these same time points rating scales on the children's symptoms were collected from parents and teachers. The test battery included non-trained tasks for WM, attention and executive functioning, these were; Span-board, Digit span, Stroop interference and Ravens progressive matrices, as well as the movement detecting system, the Optax test.

3.1.4.2 Results

Hypotheses were tested by comparing outcome score at later times (time-point two or three) for the two groups using a general linear model, controlling for age, number of days of program-use, and the baseline score. On the span-board and the Stroop test ($P < 0.002$ and $P < 0.03$ respectively), training brought the children's performance into the normal range and three months after the intervention, 90% of the training effect for the WM test remained. There was also a significant treatment effect on the reasoning test, Ravens progressive matrices ($P < 0.02$).

Only 40% of the children, who fulfilled criteria for ADHD inattentive-type before intervention did so after, based on the combined ratings from teachers and parents. Combined ratings from teachers and parents showed significant reduction of symptoms related to inattention post-intervention ($P < 0.05$; 1 SD reduction in scores, 0.9 SD at follow-up). When analyzing the parent ratings separately, they showed significant reduction in symptoms of inattention ($P < 0.002$) and hyperactivity/impulsivity ($P < 0.03$), both post-intervention and at follow-up. But when analyzing the scales from the teachers separately results were non-significant.

3.1.4.3 Discussion

In the present randomized, controlled training study, the treatment group improved significantly more than the comparison group on non-trained tests measuring visuo-spatial WM, response inhibition and complex reasoning. In addition, there was a

significant reduction in the rating scores from parents and teachers on symptoms of inattention, and on hyperactivity/impulsivity on the parent rating scales.

Inter-rater correlations are often low and difference in the ratings from parents and teachers is also seen in other studies (Wolraich et al., 2001). One possible explanation can be that because people tend to be quite rigid in their perception of others and behavioural changes take some time to detect, the mere exposure of the individual child that the parents experience are in favour to detect subtle changes (compared to teachers who often interact with 30 pupils per day.) Another possibility is that the children may behave differently at home and in school.

We saw significantly decreased hyperactivity in study III, as measured by the Optax movement detection system, but we did not so in this study. This in combination with the fact that the ratings from teachers and parents only indicated a decrease in the symptoms of hyperactivity, gives that either the training didn't have any impact on hyperactivity in this sample of children, or they were not hyperactive initially (=ceiling effects already from start) and thus the margins for improvement were less. There were also differences in the measure of interference resolution the Stroop test between the studies although improvement in both. In Study III it was the *accuracy* variable of the task that improved significantly while, in this study we found a significant decrease in response time as compared to the control treatment. Finally, one may speculate in the additive effects of medication; in study III 43% of the children in the treatment group where on medication while in the present study, medication was an exclusion criterion. Thus the combination of WM training and treatment with stimulants may strengthen each other in effecting symptoms of hyperactivity.

Conclusion

The present study confirmed the findings from the first training study; 1. WM capacity can be increased by training. 2. And that the training effect generalizes to other areas of executive functioning and behaviour. 3. The method could be implemented at other sites by other clinicians. Taken together the results suggest that systematic WM training could be of clinical use for ameliorating the symptoms in ADHD.

3.1.5 Study V- Computerized Working Memory Training - A Method of Cognitive Rehabilitation after Stroke

3.1.5.1 Introduction

Directing training at adults after brain injury may seem far away from the objective in our first two treatment studies, which where directed at children with attention deficits. However, also brain injuries cause deficits in WM and attention, which are cognitive abilities on which rehabilitation of other functions depend. Since the patient's ability to attend is a prerequisite for active participation also in other forms of rehabilitation interventions, deficits in attention are a critical issue to approach.

Stroke occurs when a blood vessel is either blocked by a clot of blood (ischemic stroke) or ruptures (hemorrhagic stroke). Oxygen, which carries oxygen and nutrients to the brain, is thus blocked from entering the affected tissue in the area where the stroke occurred. The consequence is that neurons in the affected area of the brain (the infarct) die. The part of the body and the cognitive abilities these neurons controls for gets affected. The particular abilities lost or affected depend on where in the brain the stroke occurs and on the size of the stroke (i.e., the extent of brain-cell-death). A stroke can cause many severe problems, among them paralysis, aphasia and perceptual cognitive and emotional problems. Among the cognitive symptoms, memory and attention is most frequently affected. Stroke induced deficits in attention are often severe and give impairments in both vocational performance and social functioning, and the degree of impairment on attention tasks are of central importance in predicting recovery. The rationale for most interventions is to retrain basic attentional abilities through the practice of attention tasks explicitly, for example by the use of vigilance or continuous performance tasks. Although attention and WM are closely related, there is no earlier report on WM training applied to improve attention after stroke. In this randomized controlled trial we evaluated the effect of computerized WM training in a group of ex-patients one to three years after suffering a stroke. Training task: the same version of training software as in study IV was used. One new visuo-spatial grid task was added; the inside of a box were displayed in 3D representation, there were five inner "walls" with 4 lamps positioned symmetrically on each one of them, thus in sum the task contained 20 possible target locations.

3.1.5.2 Results

As compared to a passive control group significant training effects were found on the WM tests (digit span $p < .005$, and span board $p < .05$). However, the largest treatment effect was found on the non-trained test for WM and attention; PASAT ($p < .001$) and on the serial cancellation test (RUFF 2&7) ($p < .005$). There were no significant treatment effects found on the test for episodic memory (Wordlist recall), the Stroop test or the Raven test. The lack of improvement on the episodic memory task indicates that this training method specifically targets WM and related cognitive constructs, for example attention. Besides treatment effects measured by the neuropsychological tests a self rating scale, the CFQ, was applied to evaluate possible effects on cognition in daily life. The scale includes questions on attention and memory (see study IV, table 3). Statistically significant training effects as compared to the control group were found on the CFQ as well ($p < .005$). We performed a factor analysis on the results after the training period, to see which items from the 25 item questionnaire CFQ, that correlated most with change in the self-ratings. Nine items, explaining 36% of the variance, loaded on the first same factor, these are best described as questions on absent mindedness. This subset from the CFQ alone discriminated significantly between the groups, which strengthens the findings from the neuropsychological testing; that this method targets WM and attention specifically.

3.1.5.3 Discussion

This study shows that it is possible to improve WM performance by intensive training one-to-three years after a stroke. The training effects also generalized to non-trained tests of attention as well as to cognitive functioning in daily life as measured by a self rating questionnaire. The latter result indicates that the method for WM training used here not only improve cognitive functions as measured by laboratory tests, but also influences cognitive functioning in daily life.

There are some obvious discrepancies between children with ADHD and adults with stroke. As ADHD is thought to be of genetic origin its presence in the individual is thought to be lifelong, while in stroke an injury suddenly occurs in an earlier “unaffected system”. This means that in the case of ADHD there is a long-lasting deficit which affects the individual and the formation of the nervous system

from the very beginning. In the stroke group on the other hand, the configuration of the nervous system is fully accomplished before the time of the insult. These circumstances implicate different neuronal mechanisms underlying the observable deficits at the cognitive and behavioural level; for example in WM.

The effects of a stroke on the nervous system are much more heterogeneous. The localisation varies, so do the size of the lesion and the functional sequels. Often more than one function is affected; for example a lesion in the right hemisphere can cause hemi neglect, left side paresis and WM problems. The rationale behind an intervention with WM training is thus not as straightforward as in the case of ADHD. Because of the multifaceted sequels of a brain injury, decisions on rehabilitation interventions are categorized in accordance to the patient's functional status rather than on the localisation of injury (Crafton KR, Mark AN, Cramer SC. (2003). Our experience of the clinical trial was that stroke patients could improve their WM and attentional functions independently of localization of the stroke.

Injuries in different brain areas can cause similar cognitive symptoms (Weinberger DR., 1993). A lesion might for example, affect a cortical area underlying WM, but this particular part of the brain may also be involved in other cognitive functions. There are reasons to consider overlap in the neural substrates that underlay both our primary target of intervention; WM, and other functions. A lesion, no matter where in the brain, can have widespread effects because of the interconnectivity among brain areas, in addition, chemical and metabolic functions can be globally affected. This may explain why WM and attention so frequently are affected after a stroke. It might not only depend on the localisation of the injury but rely on the global and diffuse spread of effects throughout the brain. The different neuronal background causing the WM and attention deficits in these groups suggests that there can be different underlying mechanisms for transfer effects. However, the negative finding in the LTM domain in the stroke study was expected since WM and LTM are separate constructs and the training of WM was not thought to influence LTM functioning (see §2.1.1.3). Moreover we didn't measure LTM in the other training studies which are why we can not compare the results. In the Raven's test there were ceiling effects which make it hard to interpret the results at all. The measure of inhibition and interference control, the Stroop test is known to correlate with WM, and we currently have no explanation for the negative results.

There are also other variables than anamneses and diagnoses that differ between these populations; In the case of ADHD the participants were still maturing

children, and the continuous development of the nervous system may interact with the training effects. Whereas in the stroke group the mean age of 54 years designate a mature and consolidated organization of the nervous system, which may be a limiting factor for plasticity.

Conclusions

The fact that such disparate groups as adults with stroke and children with ADHD could improve by training implies that the modus operandi of this method is general, and that other groups with WM and attention deficits also may benefit from this training.

3.1.6 Study VI- Increased prefrontal and parietal activity after training of working memory

Since the fMRI technique is harmless it allows repeated measures in the same individual, for example when implemented to track training induced changes in cortical activity. In this study we investigated if it was possible to improve WM capacity in healthy adults, if there were transfer effects to other neuropsychological tests, and if there were observable changes in task specific brain activity as a function of training. Two experiments were performed; first in three participants and then in a second experiment with eight participants, who all underwent five weeks of WM training. Brain activity was measured with fMRI before and after training. In the first experiment the training programme included both verbal and visuo-spatial WM tasks, but in the second experiment there were only visuo-spatial tasks.

3.1.6.1 Results

Neuropsychological tests. In experiment 1 improvements as compared to a passive control group ($n = 11$) were found on the span board task for all three subjects ($P < 0.001$) and on Raven's advanced progressive matrices and the Stroop task in two subjects ($P < 0.05$). In experiment 2 significant training effects were found on the Stroop test ($P < 0.05$) but not on the span-board ($P < 0.12$) and a digit-span tests (P <

0.09). The Raven test was not administrated in experiment 2. Different content in the training-programmes can explain these dissimilarities.

fMRI. Analyses were performed to find out if significant positive interactions between the factors *time* (scan 1 and 2 versus scan 3) and *task* (WM task versus control task) could be found. After training, task specific brain activity was increased in the middle frontal gyrus and superior and inferior parietal cortices, the right caudate nucleus and pulvinar thalamus, thus coinciding with the neural substrates underlying WM.

3.1.6.2 Discussion

In experiment 1 (N=3) there were increases in task specific activity after training observed in right middle frontal, right inferior parietal cortex and intra-parietal cortex bilaterally. In experiment 2 (N=8) training induced increases in activity were found in the left middle frontal gyrus and superior and intra-/inferior parietal cortex bilaterally. Subcortical increases in activity were found only in experiment 2, these were in the caudate nucleus and pulvinar thalamic nucleus. Both experiments showed increases in training related activity in prefrontal and parietal regions and decreased activity in the cingulate sulcus, thus the experiments confirmed each other. The changes in cortical activity imply training-induced plasticity in the neural systems underlying WM.

Changes in brain activity as a function of training were found in pulvinar thalamus (left side) and the head of the caudate nucleus (right side). However, the role of striatum in WM is not well understood. In a recent paper (Lewis et al, 2004) used event related fMRI to examine brain activity in a verbal WM task. They found task-specific activity in a striato-frontal network as expected. But more interestingly, when analyzing the different subcomponents of the task, subtracting the maintenance component from manipulation in WM, they found significantly increased activity only in the caudate nuclei bilaterally. In a casestudy (unpublished data from our group) on traumatic brain injury causing a lesion in the right caudate, one male subject (29 years old) undertook training one year after the injury occurred. We also applied fMRI before and after the training intervention. Significant training effects as compared to a healthy control group (N=11) were found on tests measuring WM, interference control and problem solving, but no changes were found in LTM. In addition we found one cortical area were brain activity increased as a function of training, it was in an area close to the lesioned right caudate nucleus (see figure 9).

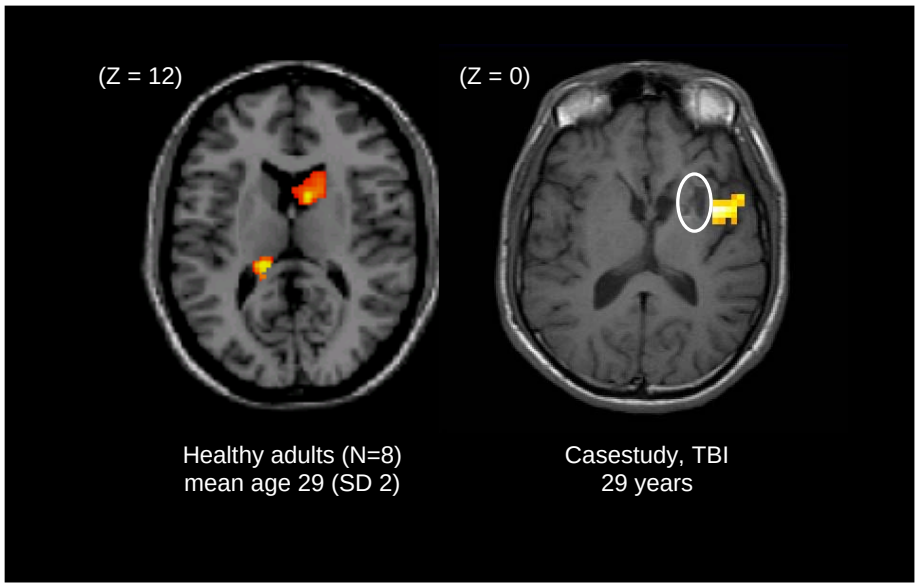

Figure 9. Left horizontal slice: Increase in brain-activity in the right caudate nucleus (and left pulvinar thalamus) following training in eight healthy subjects. Right horizontal slice: WM training following brain injury resulted in a significant increase in brain-activity next to the lesion (circled in white).

An early fMRI study in adults on activity changes over weeks of training investigated learning-related effects in motor cortex (Karni A, Meyer G, Jezzard P, Adams MM, Turner R, Ungerleider LG, 1995). Task specific cortical activity became less diffuse and increased over time in the motor cortex but there were prefrontal *decreases* in brain activity. The task specific improvement did not generalize to other movement-sequences performed by the same hand, or to the trained sequence when performed with the contra-lateral hand. This may be explained by increased routine with the task procedure and associated automation of task performance and thus less demand for top-down control were required. On the contrary the objective in our study is to influence higher cognitive functioning. We think that performance on WM tasks are hard to automatize; each of the WM trials is unique and thus associated with novelty. Since there are new configuration of stimuli sequences at every trial continuous up-dating of information in WM is required.

4 GENERAL DISCUSSION

4.1.1.1 Development

WM is a sensitive measure for cognitive deficits, perhaps because WM is central for cognition in general. For example performance on WM tests has a high correlation with scores on fluid intelligence, like reasoning and problem solving (Engle, Kane, & Tuholski, 1999; Fry & Hale, 1996; Kyllonen & Christal, 1990). The central role of WM in cognition, as well as its association with the PFC which is not fully mature before late adolescence, makes WM especially interesting in the study of cognitive development in children. The development of WM shows a prolonged course during childhood and adolescence in humans. As a function of age we found higher task specific activity in the superior frontal and intraparietal cortex during performance of the VSWM test. These neuronal substrates coincide with the substrates that exert influence over other cortical areas. Activity increase in the PFC also showed up in two later developmental studies on impulse control (Durston S, Thomas KM, Yang YH, Ulug AM, Zimmerman RD, Casey BJ (2002) and interference resolution (Adleman NE, Menon V et al 2002). Thus, the development of these areas may underlie the development of VSWM, among other cognitive functions, during childhood.

4.1.1.2 Training of working memory

Our results from study II, on the sensitivity of the VSWM test in discriminating between children with and without ADHD support the hypothesis on WM as a central deficit in ADHD. This finding encouraged us to investigate if intervention on this core deficit could; (1) make impact on WM and (2) generalize to influence other areas of cognitive functioning. The hypotheses were tested by inventing a computerized method for WM training, the effectiveness of which was evaluated in children with ADHD in two consecutive studies. In the first pilot study (N=14), there were significant improvements in the treatment group as compared to the control group on the trained WM test, on the non-trained WM tests (Span-board and Digit span), as well as on other non-trained tasks for executive functioning and as measured by a movement detection system; Optax. The results on the cognitive tests were later

replicated in a larger sample (N=44), in a randomized, double-blind, placebo-controlled multi-center trial. In the latter study we also found generalisation of training effects to decreases in symptoms as measured by parent's and teacher's rating scales on inattention and hyperactivity/impulsivity. However the results on the Optax test was not confirmed.

We further investigated if other patientgroups with significant WM deficits could benefit from WM training. Participants suffering a stroke one to three years earlier were recruited to undertake the training regimen. Although adults and with another aetiology the training group improved significantly in WM capacity and attention as well as on cognitive symptoms in daily life, as measured by a self rating questionnaire.

There are today, very few studies on cognitive training in ADHD (see § 1.6.1.2 and 3) thus there are not many other studies to compare our results with. However, this is a new research field and among others, Michael Posner and his group at the Sackler institute in New York has initiated research on training of attention and executive functioning in children with attention deficits by the use of their own training software. The group also investigates the developmental course of executive control in young children, both anatomically and functionally, and furthermore explore the role of attention and executive control in the acquisition of higher level cognition, such as reading (Posner & Abdullaev, *in press*) and counting (Temple E, Posner MI, 1998).

4.1.1.3 Neuronal correlates of training

In order to explore the neuronal correlates of improvement of WM, healthy young adults were recruited and underwent fMRI before and after a five week long training period. Task specific increases in brain activity were found in prefrontal and parietal cortex. These regions coincide with the cortical areas known to underlie WM functioning. The increases in task-specific cortical activity found in the present study indicate training-induced plasticity in the adult nervous system. Intra-individual changes in brain activity as a function of training in adults may or may not be mediated by the same mechanisms that mediate developmental changes in WM. The extent and intensity of cerebral activity associated with a WM in children may alter as they mature. This might be due to physiological developmental mechanisms such as increases in myelin, or neuronal selection and dendritic branching, which results in a

more efficient communication in the neuronal system. The training-related changes in neuronal activity observed in adults may depend on other mechanisms, since they already have a mature nervous system. One way to answer this question would be to investigate if children after intense training would show the same brain activity pattern as adults without exceeding practice in the task. However, as we currently have no fMRI data on children after WM training we can only compare the results on WM related changes in brain activity in children's cognitive development and those found in adults after training of WM. When comparing the fMRI data on adults after training, with data from WM development in children, there are some similarities in the topographic pattern of activity peaks but also some deviations. In children, we found increases in activity both as a function of age and as a function of WM capacity in superior frontal sulci bilaterally (-24, -4, 52 and 30, 0, 52) and also in an additional area in the left frontal lobe (-28, 6, 60). In adults, there were increases in medial frontal sulci, predominantly on the left side (-26, 22, 56). When considering only capacity-related changes in children, across the age groups, there were a significant cluster in left superior frontal sulcus (-26, 4, 60) showing up. Decreases in brain activity were found in the right inferior frontal sulcus both in children (42, 4, 40) and in adults (46, 28, 34), although in children as a function of age and in adults as a function of training. In the intraparietal cortex in the left hemisphere, there were activity related increases in both children (-50 -46 56) and adults (-52 -44 28) correlating with WM capacity. To summarize; we found similar parietal increases in both children and adults as a function of increasing WM capacity, but the frontal increases were not comparable, the activity peaks were located more anterior and inferior in the adult PFC.

4.1.1.4 Possible explanations of transfer effects

When considering the results from the training studies we can see that such disparate groups as children with ADHD, middle-aged adults after stroke and young healthy adults can improve their WM capacity, although there were different outcomes in the measures of transfer effects between groups. Since WM and attention are overlapping concepts our assumption is that training of WM could influence performance on other attention demanding tasks. Anatomically, this association could be explained by overlapping parts of cortex used for WM and other executive functions. For example the same areas in the PFC and the parietal cortices, underlies

development of both visuo-spatial WM capacity and performance on an interference resolution task (Stroop) (Adleman NE, Menon V et al 2002). Moreover, given that top-down signals from PFC enhance internal representations in posterior parts of the cortex, efferent signals from the PFC may have different functional implications, depending on witch cortical region that is under the influence of top-down control from the PFC.

WM is central in attention, executive functioning and interference control, thus the influence of WM on these other cognitive constructs can explain why training of WM specifically can generalize to change performance also on other tests of executive functioning. The contribution of WM in different cognitive tasks as well as its multimodal features (Sylvester CYC, Wager TD et al, 2003) may be the explanation for the quite unique transfer effects seen after WM training. Actually the transfer effects found in the training studies from our group support the central role of WM in cognition.

4.1.1.5 Further questions

4.1.1.5.1 Reconsidering psychiatric diagnostics?

WM seems to be affected in a number of psychiatric disorders (e.g. in schizophrenia). Therefore, more research needs to be done in investigating the sensitivity of WM tests also in other diagnoses. The comparison of relative sensitivity and specificity of different tests could lead to a more profound knowledge of the characteristics of ADHD as well as its commonalities and differences with the features of other diagnoses. Moreover, one may consider what information can be gained by a neuropsychological test that cannot be acquired by biological, endocrinological or neuroanatomical measures? To answer this we have to bear in mind that there is no single biological marker for most psychiatric diagnosis. Today the classification systems in psychiatry (DSM-IV) describe disorders whose symptoms vary extensively between individuals. Psychiatric diagnoses might be more informative if described in terms of individual profiles of cognitive functioning. By breaking down psychiatric classifications and diagnoses to its subcomponents one could perhaps better characterize the individual's difficulties as well as obtain clues on the genetic origin. Taken together this procedure could result in more straightforward diagnostics and treatment. A useful concept in line with the

individual-profile-diagnostics in the study of complex neuropsychiatric disorders could be to identify endophenotypes (Gottesman, I & Gould, TD, 2003). The term endophenotype is here defined as a measurable neuropsychological characteristic which is thought to mediate between neurobiology and manifest behaviour. There are other terms with the same meaning, such as biological marker or subclinical trait, but we have chosen to use the term endophenotype to denote the aim of identifying the linkage between genetics, cognition and behaviour. It has been suggested that WM constitutes an endopehnotype for ADHD (Castellanos FX & Tannock R, 2002). An endophenotype is thought to be heritable, state-independent (manifests in an individual whether or not illness is active) and found in non-affected family members at a higher rate than in the general population (Leboyer M, Bellivier F et al, 1998). In addition to the inherent complexity of psychiatric disorders, which probably have polygenetic origins, the brain is incredibly multifaceted. The brain is subject to complex interactions not just among genes and neurons but also is under the influence of our experiences (Kandel ER, 1998-469). Therefore, endophenotypes are also thought to include environmental influences on behaviour.

4.1.1.5.2 Explore possible neuronal correlates underlying transfer effects

Overlapping activity in cortical areas during performance of different tasks could provide clues on possible transfer mechanisms. For example task related activity were found in the same area of the (left) prefrontal cortex during performance of two executive tasks, one of shifting attention and the other on interference resolution (Sylvester, C-Y C., Wager, TD., Lacey, SC., Hernandez, L., Nichols, TE., Smith, EE. & Jonides, J., 2003). This study points out that one way to test the hypothesis on common cortical areas underlying different cognitive functions, is to let the same subjects, while being scanned, perform those tasks in which transfer effects are found (in our case the Stroop, Raven and PASAT tests) and then analyze if task specific activity overlap, and if so in which cortical areas. Moreover it could be interesting to follow inter-related developmental changes in brain activity by implementing the same concept in children. It would also be interesting to measure the durability of gained capacity increases as well as related changes in brain activity by scanning the same participants who underwent training, again after six and twelve moths respectively.

4.1.1.5.3 Further development of the training method

More effort should be put in exploring how to optimize the training method. This can be done for example by analyzing the accumulated data on training results to find out what factors estimates successful training. This knowledge can also be used to modify the training programme to fit the individual's needs by the adjustment of content, amount as well as duration of training.

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