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PROBING AND PUSHING POTENTIAL

Genetics, development and training of cognitive functions

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ABSTRACT

Capacities of cognitive functions increase considerably during childhood and adolescence. This development is of importance as poor development can predict lower performance on academic skills. Furthermore, severe impairment is related to symptoms of many neuropsychiatric disorders such as attention deficit/hyperactivity disorder (ADHD). These observations have lead to a great interest within the research community to understand 1) underlying mechanisms that influence cognitive development, and 2) factors that can improve cognitive capacity. This thesis aims to increase understanding of these topics, focusing on two specific cognitive functions: working memory (WM) and non-verbal reasoning (NVR).

Study I investigated the effects of polymorphisms within certain candidate genes on WM performance and also brain function and structure in a sample of typically developing children and adolescents. We found that a polymorphism within the *SNAP25* gene was significantly associated with WM capacity, ADHD symptoms in males as well as activity and grey matter density within the posterior cingulate cortex. This brain activity in turn correlated with degree of ADHD symptoms. Brain activity significantly predicted ADHD symptoms two years later.

Studies II and III investigated how reasoning ability and WM can be improved with training. Study II assessed a newly developed NVR training programme in combination with a previously studied WM training programme in a sample of typically developing 4-year-old children. Training NVR resulted in significant improvements in performance on a measure of fluid reasoning and training of WM significantly improved performance on WM measures. There was limited transfer between the two different functions. Study III assessed the same training programme in children with intellectual disability. In this group, there was a large variance in progress observed during training and we found that this variance was important for predicting improvements following training. Baseline capacities, gender, and co-morbidity with additional diagnoses predicted the degree to which the children with intellectual disability improved during training. The study findings highlight the importance of inter-individual differences for understanding the effects of cognitive training.

Finally, **Study IV** showed that variations within a gene coding for dopamine transporters is associated with inter-individual differences in the degree of improvements observed after cognitive training.

Together, these studies illustrate that the genetic variants we are born with influence the development of our brains and cognitive abilities, and that this development can be influenced by environment and experience such as cognitive training. Importantly, genes and environment interact, with our pre-determined genetic setup influencing our susceptibility to environmental influence.

LIST OF PUBLICATIONS

I. **Söderqvist, S**., McNab, F., Peyrard-Janvid, M., Matsson, H., Humphreys, K., Kere, J., & Klingberg, T. (2010). The SNAP25 gene is linked to working memory capacity andmaturation of the posterior cingulate cortex during childhood. *Biol Psychiatry, 68*(12),1120-1125.

II. Bergman Nutley, S., **Söderqvist, S**., Bryde, S., Thorell, L. B., Humphreys K.,& Klingberg,T. (2011). Gains in fluid intelligence after training non-verbal reasoning in 4-year-old children: a controlled, randomized study. *Dev Sci, 14*(3), 591-601.

III. **Söderqvist, S**., Bergman Nutley, S., Ottersen, J., Grill, K.M., Klingberg, T. Computerized training of non-vernal reasoning and working memory in children with intellectual disability. *Submitted manuscript*

IV. **Söderqvist, S**., Nutley, S. B., Peyrard-Janvid, M., Matsson, H., Humphreys, K., Kere, J., & Klingberg, T. (2012). Dopamine, working memory, and training induced plasticity: Implications for developmental research. *Dev Psychol, 48*(3), 836-843.

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit/Hyperactivity Disorder
WM	Working Memory
NVR	Non-verbal reasoning
COMT	Catechol-O-methytransferase
PFC	Prefrontal Cortex
DAT1	Dopamine Transporter
DRD4	Dopamine receptor D4
DRD2	Dopamine receptor D2
dlPFC	Dorsolateral prefrontal cortex
Gf	Fluid intelligence
Gc	Crystallised intelligence
DNA	Deoxyribonucleic acid
PET	Positron emission tomography
SNP	Single Nucleotide Polymorphism
MRI	Magnetic resonance imaging
VBM	Voxel based morphometry
fMRI	Functional magnetic resonance imaging
BOLD	blood-oxygen-dependent
SNAP25	Synaptosomal-associated protein at 25kD
GMD	Grey matter density
T1	Time point one
T2	Time point two
DMN	Default mode network

1 INTRODUCTION

1.1 WORKING MEMORY

1.1.1 Concept

Working memory (WM) is the ability to hold information in mind for a short period of time. It also includes the ability to manipulate, or work, with this information. For example, recalling a sequence of digits requires you to hold information in mind, but recalling the digits in the reversed order involves both holding and manipulating the information in mind. This ability is limited, as is apparent in time (immediate memories last less than 20 seconds) (Goldman-Rakic, 1996) and in the number of separate items that can be remembered (typically around seven for young healthy adults) (Miller, 1956). WM is accordingly the process that allows us to remember information that we have just received, before this information is either further processed or forgotten.

1.1.2 Cognitive models

The most commonly referred to cognitive model of WM was introduced Baddeley and Hitch in the 1970s (Baddeley & Hitch, 1974). The original model proposed a three-part system allowing for storage and manipulation of information in memory with a limited capacity. The three parts of the original model were a visuo-spatial sketchpad storing visuo-spatial information, a phonological loop storing verbal information, and a central executive, functioning as a general coordinator directing attention and allowing for manipulation of the information currently held in the two storage systems. In 2000, Baddeley suggested a revised version of the model with an added component called the episodic buffer (Baddeley, 2000). The role of the episodic buffer is suggested to integrate information from different modalities and to interact with long term memory.

There have been a number of other competing models suggested. One of the most influential is that by Cowan first proposed in 1988 (Cowan, 1988). In this model, WM does not have a storage capacity itself; rather it involves activation of contents within long term memory by directing the focus of attention to this content. This model is supported by observations that different networks of brain regions are activated for WM tasks that require the storage of different types of information (D'Esposito, 2007).

1.1.3 Biological mechanisms

Extensive research has been carried out investigating WM on a cellular level. These studies have used cell recordings that measure activity in single brain cells, typically in monkeys, while the animal is performing a WM demanding task. Such recordings have identified cortical cells showing sustained activity during memorizing of information (Fuster, 1973; Fuster & Alexander, 1971). These cells have been called “memory cells” as they are believed to provide a neurological mechanism for storage in WM.

1.1.3.1 Role of dopamine

In humans evidence for the role of dopamine for WM function comes mainly from pharmacological and genetic studies. For example, methylphenidate, which is a commonly prescribed medication for patients with Attention Deficit/Hyperactivity Disorder (ADHD), acts by blocking the reuptake (and thereby increasing the available concentrations) of dopamine and norepinephrine. Methylphenidate increases performance on WM tasks, particularly visuo-spatial WM (Mehta, Goodyer, & Sahakian, 2004; Mehta et al., 2000; Solanto, 1998). There are pharmacological studies investigating the effects of dopamine more specifically by manipulating dopamine D1 and D2 receptor activity. These studies point consistently to an involvement of the D1 receptors, whereas findings regarding the D2 receptors are less coherent (Kimberg & D'Esposito, 2003; Kimberg, D'Esposito, & Farah, 1997; Luciana & Collins, 1997; Muller, von Cramon, & Pollmann, 1998). Genetic studies also point to the importance of dopamine for WM ability in humans. Candidate genes studies looking at the effect of genes involved in the dopaminergic system on WM performance and related brain activity have found significant associations for the *COMT* gene (particularly important for dopamine clearance in the prefrontal cortex, PFC), the *DAT1* gene (important for dopamine clearance in several brain areas including the basal ganglia), the *DRD4* gene (coding for the dopamine receptor 4), and the *DRD2* gene (coding for the dopamine receptor 2) (Barnett, Heron, Goldman, Jones, & Xu, 2009; Dumontheil et al., 2011; Froehlich et al., 2007; Fuke et al., 2001; Mill, Asherson, Browes, D'Souza, & Craig, 2002; Stelzel, Basten, Montag, Reuter, & Fiebach, 2009; Stollstorff et al., 2010; Xu et al., 2007)

There is further evidence for the role of dopamine for WM functioning on a cellular level. Much of this research has been performed on cells in the PFC that are distinctively active when stimuli of a certain spatial location are presented. As this activity is remained during the delay period until a response has been made, this is believed to be the cellular basis for visuo-spatial WM. The activity of neurons displaying memory fields has been found to be dependent on available dopamine levels (Williams & Goldman-Rakic, 1995). Stimulating dopamine D1 receptors improves WM performance, and this has been shown to occur as a result of these cells becoming more specific in their response; by decreasing the response to stimuli with a non-preferred spatial location the tuning to the preferred direction is improved (Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007). Effects of D1 receptor stimulation on improved WM performance can last for as long as a year following treatment (Castner & Goldman-Rakic, 2004; Castner, Williams, & Goldman-Rakic, 2000).

The effects of dopamine on cellular functioning, and extending to behavioural performance, typically follow an inverted U-curve pattern. With performance represented on the y-axis and level of dopamine on the x-axis as illustrated in figure 1. The inverted U-curve illustrates that there is an optimal level of dopamine that is

advantageous for performance and that levels above or below that will have impairing effects (Seamans & Yang, 2004). This also means that baseline levels of dopamine might influence the effects of manipulations to the dopamine system. There is for example some evidence that polymorphisms of the *COMT* gene that influence dopamine levels in the PFC predicts changes in WM related brain activity after treatment with amphetamine (Mattay et al., 2003). Further, natural changes in baseline dopamine levels, as occurring during development, can lead to differentiating consequences of different genotypes as has been shown for the *COMT* gene (Dumontheil et al., 2011).

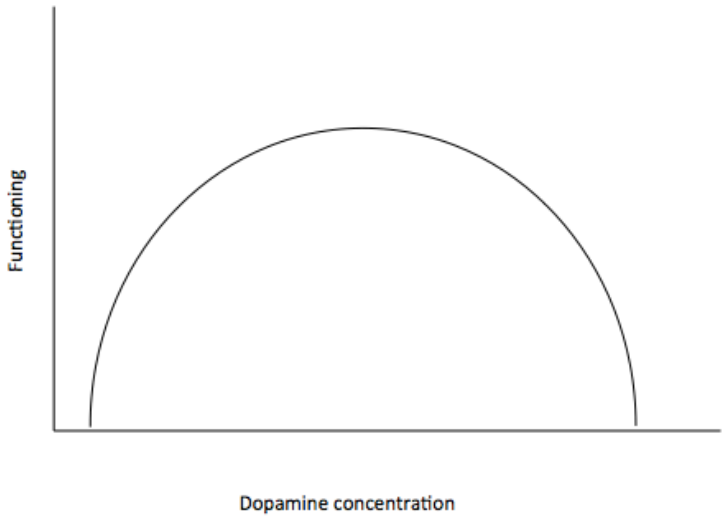

Figure 1. A schematic illustration of inverted an U-curve pattern associated with dopamine function.

1.1.3.2 Neuroimaging

Functional magnetic resonance imaging (fMRI) studies of WM related activity consistently show activity in parietal cortex (particularly intraparietal sulcus), and frontal cortex (particularly the superior frontal sulcus and anterior parts of the dorsolateral PFC, dlPFC) (Klingberg, Forssberg, & Westerberg, 2002a; Todd & Marois, 2004; Vogel & Machizawa, 2004). The precise localisation of activations depends on the type of stimuli to be remembered. This has been suggested to reflect that maintenance of information involves recruitment of areas where such information is already stored (D'Esposito, 2007). Activity in the dlPFC is considered to provide top-down control, and in this sense can be considered an executive control, biasing what information is entered and maintained in more posterior regions. Indeed, activity in the PFC together with activity in the basal ganglia has been related to the ability to filter out or ignore irrelevant information, which is important for WM capacity. Basal ganglia activity seems to be particularly important for this as it predicts the amount of irrelevant information stored in the parietal areas, which in turn predicts WM capacity (McNab & Klingberg, 2008). A later study by Edin et al. (2009) using computational modelling has suggested that one role of the dlPFC during the preparatory stage (at cue, before stimulus presentation) is to execute a boosting effect. According to this model,

increasing excitatory input from the PFC to parietal areas increases storage capacity. fMRI data supports the idea that enhanced functional coupling between dlPFC and parietal areas (intraparietal sulcus in particular) increases visuo-spatial WM capacity. These findings suggest that two types of capacities are important for determining WM capacity: first, the control mechanisms of filtering, boosting or otherwise biasing processing that is believed to be carried out within PFC and basal ganglia areas and second, the capacity for storage believed to be carried out in more posterior cortical areas and possibly also posterior parts of the PFC.

1.2 REASONING ABILITY

Reasoning ability refers to the ability to think logically and to find rules and patterns that allow problem solving in novel situations (Ferrer, O'Hare, & Bunge, 2009). This ability is a crucial aspect of the more general concept of intelligence. A fundamental observation underlying this literature is that, when measuring cognitive abilities a pattern of positive correlations typically occurs in which better performance on one task predicts better performance on another. These correlations are believed to result from a common factor that has been called general intelligence, or *g* (Neisser et al., 1996). There is currently no common agreement on what this factor *g* represents but many suggestions have been made such as it representing mental energy, a general reasoning ability or that it results from a statistical phenomena (as discussed in Neisser et al., 1996).

In the 1960s Horn & Cattell (1966) made a broad distinction between two subcategories of *g,* one called fluid intelligence (*Gf)* and one called crystallised intelligence (*Gc*). *Gf* reflects the ability to identify rules and relationships in a novel situation, unrelated to previously learned knowledge. *Gc* on the other hand reflects such learned knowledge, such as general facts and vocabulary. Ian Deary and colleagues have described *Gf* as intelligence-as-process, in contrast with *Gc* as intelligence-as-product (Deary, Penke, & Johnson, 2010). However, the acquisition of new knowledge depends on our ability to process it in the first place and therefore *Gc* is dependent on *Gf*.

These constructs have traditionally been measured using latent variable analyses in which, in the case of fluid intelligence, *Gf* is represented as a latent construct derived from many different measures of reasoning ability. Reasoning ability, examined in Study II and Study III of this thesis is measured using tests that load highly on the *Gf* construct. We chose to only talk about *Gf* in Study II in the cases where we used a latent variable approach. As we used visuo-spatial tasks we call the tasks non-verbal reasoning (NVR).

1.3 DEVELOPMENT OF WORKING MEMORY AND REASONING

1.3.1 Development of cognitive capacity

WM capacity increases during childhood and adolescence, with a more rapid increase occurring in the earlier years (Gathercole, Pickering, Ambridge, & Wearing, 2004), see figure 2 for an example. Some of the increase occurring before adolescence might be due to an increased use of strategies. For example, it has been shown that before the age of seven, rehearsal of verbal information does not occur spontaneously. This could explain the lower performance in both verbal and visuo-spatial WM, as rehearsal is also often used for visual information that can be encoded in verbal information. Development of visuo-spatial and verbal abilities occurs in parallel. Although visuo-spatial and verbal abilities are related, there is evidence that suggests they also have unique components (Gathercole et al., 2004).

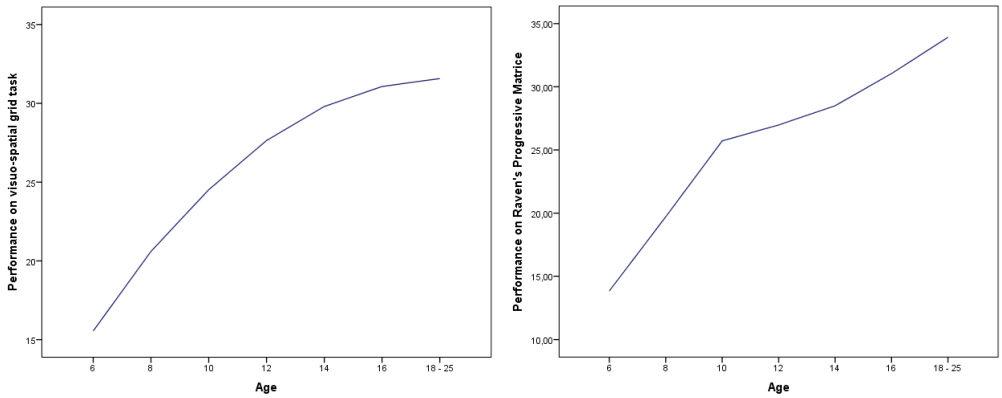

Figure 2. Performance on a visuo-spatial WM task (to the lef) and NVR (Raven's progressive matrices, to the right) across age groups in a typically developing sample (the "Brain Child" sample, studied in Study I).

Development of reasoning ability follows a similar pattern to the development of WM, showing a more rapid development during childhood, a slower increase across adolescences and into early adulthood, followed by decline (Ferrer et al., 2009). Such age differences in performance on the Raven's progressive matrices are illustrated in figure 2. Although absolute measures of reasoning increases during development, relative measures (an individual's level of performance in relation to his or her age group) tend to remain stable (Neisser et al., 1996).

1.3.2 Development of the brain

The improvements in cognitive functions seen during development are also linked to the maturation of the brain (Klingberg, 2006; Spencer-Smith & Anderson, 2009). For WM, children show differential activity within both parietal and frontal cortices compared with adults (Klingberg, 2006; Klingberg et al., 2002a). These are the same areas that distinguish differences in WM capacity within a group of adults (McNab & Klingberg, 2008; Todd & Marois, 2004; Vogel & Machizawa, 2004). Similarly,

differences in rostrolateral and dorsolateral PFC, as well as parietal cortex have been observed in children compared to adults while performing a reasoning task (Crone et al., 2009; Dumontheil, Houlton, Christoff, & Blakemore, 2010).

The structure of the brain undergoes significant changes throughout the childhood and adolescent years. White matter volume continues to increase as a result of increasing myelination, while the development of grey matter follows a more complicated pattern. Grey matter volume increases during early childhood years. Later in development this is followed by a pruning process, a fine-tuning of the neuronal networks, in which connections that are not commonly used are removed. This results in a thinning of grey matter. Thus in most brain areas the development of grey matter follows a non-linear, quadratic or cubic, development pattern (Johnson, Blum, & Giedd, 2009; Shaw et al., 2008). The time frame of development differs for different areas of the brain, generally occurring earlier in posterior parts. In the most posterior brain regions, thickness of grey matter reaches its peak around the age of 7 and 8 years, whereas in more frontal areas, it has not fully reached its peak before the age of 12 (Johnson et al., 2009; Shaw et al., 2008). These results represent group averages, but it has been shown that developmental trajectories differ between individuals and that these differences are reflected in differences observed in cognitive ability. For example, children who score high on intelligence measures have been shown to have more drastic developmental trajectories, with an initially greater grey matter thickness being followed by a more intense pruning, resulting in a steeper decrease in grey matter thickness. This results in a shift in relationship between intelligence and grey matter thickness, with a positive correlation in early years, that later (after approximately 14 years of age) shifts to a negative correlation (Shaw et al., 2006). Another trait linked to the development of grey matter thickness is ADHD. In a study of over 200 children with ADHD and as many typically developing controls, it was demonstrated that although the developmental trajectories were similar across groups, the children with ADHD reached their peaks in grey matter thickness later than controls (Shaw et al., 2007). This suggests that ADHD is related to a delay rather than a deviance in brain maturation. Interestingly this delay was most prominent in the PFC, which, as discussed earlier, is important for WM and other cognitive functions.

1.4 RELEVANCE OF STUDYING WM

1.4.1 Relation to other cognitive abilities

Although development of cognitive functions such as WM and reasoning is to a great extent predicted by age, large differences are apparent within age groups. Figure 3 shows the standard deviations on performance on a visuo-spatial WM task for different age groups of typically developing children and adolescent, illustrating how much data normally varies within age groups.

This variance can have important consequences as WM capacity is strongly related to many other cognitive abilities such as reasoning ability (Conway, Kane, & Engle, 2003; Engle, Tuholski, Laughlin, & Conway, 1999; Kane et al., 2004), attention (Kane, Bleckley, Conway, & Engle, 2001) as well as level of distraction and inhibitory control (Conway, Cowan, & Bunting, 2001; Kane et al., 2001). Part of such relations can be understood as an involvement of WM in tasks measuring these other abilities, for example that one has to remember the goals and rules of these tasks. In particular tasks measuring reasoning ability often involves many different complex rules that has to be held in mind while solving the task. This however does not completely explain the relation between WM and reasoning, as strength of correlations between WM performance and performance on a commonly used measure of reasoning ability, Raven's progressive matrices (described in more detail in the methods section), does not depend on the memory load required in each item (Unsworth & Engle, 2005).

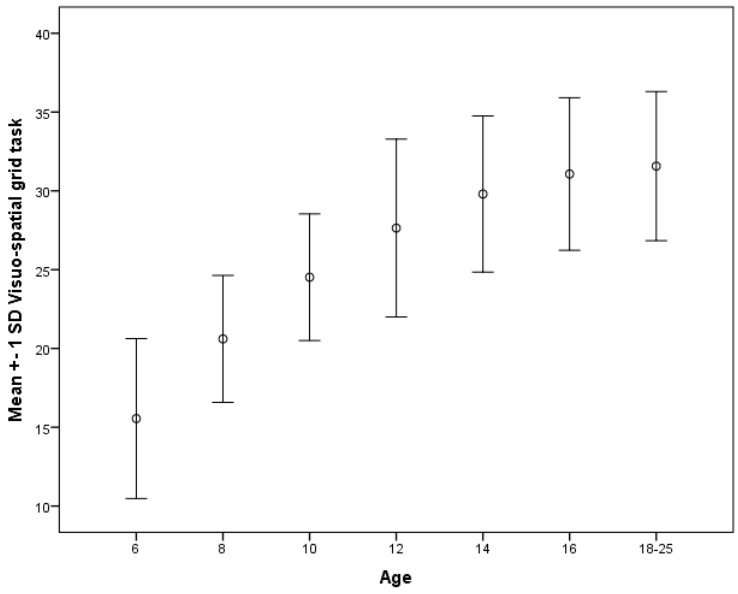

Figure 3. Standard deviation on performance on a visuo-spatial WM task for different age groups.

1.4.2 Importance for academic achievement

In addition to being related to performance on cognitive abilities, WM is also important for academic performance. This is unsurprising considering its close association with attention, but WM also more specifically relates to academic skills such as reading and mathematics (St Clair-Thompson & Gathercole, 2006). Not only is there a relation between current WM capacity and academic performance, but WM capacity and related brain activity at an early age can actually predict a child's academic performance a few years later (Bull, Espy, & Wiebe, 2008; Dumontheil & Klingberg, 2012; Gathercole, Leanne; Pickering, 2003). These findings make understanding WM, how it functions and how it can be improved important. By understanding how it

develops and how we can identify children with low WM at an early stage, we can target interventions that can hopefully prevent these children from having a poor academic development as a consequence. What is important to note is that most of these findings are based on samples of typically developing children, showing that even small differences in WM capacity is of importance, and suggesting that improving WM capacity can be beneficial even for individuals who would be considered within the range of typical development.

1.4.3 Clinical relevance

Larger deficits in WM capacity are observed in children diagnosed with developmental disorders such as ADHD and intellectual disability (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Van der Molen, Van Luit, Jongmans, & Van der Molen, 2009), as well as many other neuropsychiatric disorders such as Schizophrenia (Goldman-Rakic & Selemon, 1997). Children with intellectual disability commonly show deficits in WM. Some evidence suggests that these children have larger deficits in verbal WM (Van der Molen et al., 2009). Children with ADHD on the other hand, often show larger deficits in visuo-spatial WM capacity (Martinussen et al., 2005). Deficits in WM have been suggested to be an endophenotype for ADHD, meaning that these deficits might underlie some of the behavioural symptoms observed in patients with ADHD (Castellanos & Tannock, 2002). This suggestion is interesting from several perspectives. First, it suggests that learning more about WM and its function in the brain can also improve our knowledge regarding symptoms that are related to impairments in WM, such as symptoms of ADHD. Second, if WM deficits are partly causing behavioural problems, improving WM might also improve on these problems.

1.5 FACTORS AFFECTING WORKING MEMORY AND REASONING ABILITY

1.5.1 Genetic influence.

Monozygotic (identical) twins are the only pairs of humans who share their genetic setup completely with another individual, as identical twin-pairs have identical deoxyribonucleic acid (DNA). Dizygotic (fraternal) twins on the other hand, are like any other sibling-pair when it comes to DNA and they share approximately 50% of DNA. However, monozygotic and dizygotic twins are believed to be more similar when it comes to the amount of environment they share with their sibling, including much of the environment in the womb. This assumption is commonly used in studies aiming to separate how much a trait is influenced by genetic factors on the one hand, and environmental factors on the other. The increased similarity of a certain trait in monozygotic twins compared to dizygotic twins can then be seen as an indication of the amount of genetic influence underlying that trait. Using these methods of investigation, both WM and measures of intelligence have been shown to be under a large genetic influence (Friedman et al., 2008; Luciano et al., 2001). Furthermore, portions of WM

related brain activity are explained by genetic variance (up to 60% but averaging around 30%) (Blokland et al., 2011).

Considering the large genetic influence on cognitive functions, relatively little is know about the specific genes that are underlying variability in WM. However, as mentioned above in section 1.1.3.1 some candidate genes have been identified, many of which are involved in the dopaminergic system such as *COMT, DRD4, DRD2* and *DAT1*.

As mentioned above, WM has been suggested as an endophenotype for ADHD, meaning that WM might be an intermediate factor between biological causes (such as genetic effects) and behavioural symptoms associated with ADHD (Castellanos & Tannock, 2002). We based our selection of candidate genes in Study I on this idea and included genes that had previously been associated with ADHD with the hypothesis that some of these might also affect WM.

1.5.2 Environmental factors

The environment in which we are brought up is known to influence the way our brains and cognitive functions develop. This can be in a positive direction; an enriched or highly stimulating environment, social interaction and physical activity are some examples of environmental factors that have been shown to have positive effects on the brain and cognition (Hillman, Erickson, & Kramer, 2008; van Praag, Kempermann, & Gage, 2000). However, it can also have negative effects and environmental factors that have been shown to have a negative influence on brain and cognition include, maternal stress during pregnancy, poor parental care during childhood, emotional or physical trauma and birth complications (Caspi & Moffitt, 2006).

Another way of looking at the effects of environment (in comparison with genetic effects) is to look at the effects of behavioural interventions, in which an effort is made to change the environment for an individual. Interventions often have the benefit of being distinct in time and therefore provide an opportunity to get precise measures of changes that result from the intervention (by measuring performance before and after the intervention). One type of such interventions, or manipulation of environment, and a large focus of this thesis is cognitive training.

1.5.2.1 Cognitive training

Methods for improving memory has traditionally been focused on applying mnemonics and other strategies that employ use of semantic encoding of information and typically rely on long-term memory to a large extent. This type of training has been called explicit training (Klingberg, 2010). One example of this is the classic study by Ericsson et al. published in Science in 1980. The study included one undergraduate student, S.F., who during 20 months practiced a digit span task requiring memorizing as many digits

as possible. The student's initial capacity was, as expected, around 7 digits. After a total of 230 hours of practice, he managed to increase this capacity to remembering an impressive 80 digits. It was reported that he used a number of different strategies to achieve this. In particular S.F. developed a strategy that allowed him to "chunk" single digits to groups of four digits, thereby decreasing the information to keep in mind. In addition, he linked these numbers to meaningful information stored in his long-term memory, as S.F. was a running enthusiast this information happened to be running times. The problem with this explicit training approach was revealed when the student was later presented with lists of letters to remember. This simple manipulation of the task caused his performance to drop back to baseline levels, and thus his improvements showed no transfer to other memory tasks. In addition the performance on the digit span task relied on the extent to which the digits could be coded into meaningful sequences and manipulation of this also caused his performance to drop back to baseline performance. The authors make a distinction between capacity of memory and memory skills. Based on their results they conclude that it is not possible to increase the capacity of (short-term) memory, but that "with an appropriate mnemonic system and retrieval structure, there is seemingly no limit to improvement in memory skill with practice." (Ericcson, Chase, & Faloon, 1980). Thus the skill or strategies developed are beneficial for solving tasks where it is possible to use the specific strategies, and such skills can indeed be very useful in everyday life. However the improved performance cannot be viewed as an increase in capacity as no increased performance is observed on tasks that do not allow for the usage of these specific strategies (even though they rely primarily on WM function). In other words there is no transfer of the improvements observed to other tasks.

However, by not taking Ericson et al. words for truth and giving up on the idea that capacity can be improved, researchers have instead started to investigate an alternative approach to training. This type of training has been called implicit training and focuses on repetitive practice on tasks without teaching of strategies (Klingberg, 2010). By increasing the level of difficulty to levels that are close to the capacity limit of the participants, the training involves a constant challenge of this limit. The idea is that by provoking such an intense usage and challenge of the capacity, the brain functions involved will be strengthened. By strengthening the functions *per se,* transfer to other tasks relying on the same brain functions is considered more likely.

One such training programme was developed by Klingberg and his colleagues (Klingberg et al., 2005; Klingberg, Forssberg, & Westerberg, 2002b). This computerised training programme aims at improving WM function and includes WM demanding tasks both within visuo-spatial and verbal domains (this programme is now provided by Cogmed). It employs an algorithm that adapts the difficulty level of tasks depending on the participant's individual performance, such that difficulty (number of items to be remembered) is increased if the participant answers correctly, but decreased if he or she answers incorrectly. This leads to a training that is always at a challenging level for each individual. This characteristic of adaptive difficulty is considered so important that the opposite, low-level non-adaptive training, has commonly been used

as control conditions in studies by Klingberg and others (including studies II, III and IV in this thesis). This approach provides a very strict control condition in which other factors that can potentially improve cognitive performance such as focusing on a computer task for a sustained period and increased one-on-one contact with an adult, are held constant. Any differences in improvements between these groups can then with greater certainty be said to result from the active training component. In the initial studies children trained with this programme (either the adaptive or non-adaptive control version) for approximately 40 minutes a day, 5 days a week for 5 weeks.

Based on the evidence for WM deficits in ADHD discussed above, children and youth with ADHD were the first group in which this training programme was evaluated. Results showed that the programme was successful in improving WM on tasks that were dissimilar to those trained upon (Klingberg et al., 2005; Klingberg et al., 2002b). Thus, the improvements in WM transferred to other measures of WM suggesting that the WM capacity of participants had improved. In addition transfer was observed to tasks beyond WM, with improvements seen on measures of both non-verbal reasoning and inhibition. Furthermore, increased WM capacity also lead to a reduction in symptoms of inattention in every-day life. Following these promising results a number of studies have demonstrated improved WM capacity following training in other populations including healthy children and adults (Dahlin, Neely, Larsson, Backman, & Nyberg, 2008; Jaeggi, Buschkuehl, Jonides, & Perrig, 2008; McNab et al., 2009; Olesen, Westerberg, & Klingberg, 2004; Thorell, Lindqvist, Bergman Nutley, Bohlin, & Klingberg, 2009), children with low WM capacity (Holmes, Gathercole, & Dunning, 2009), children born pre-term (Lohaugen et al., 2011), children with intellectual disability (Van der Molen, Van Luit, Van der Molen, Klugkist, & Jongmans, 2010), and adults recovering from stroke (Westerberg et al., 2007).

Although studies repeatedly show that WM capacity is improved as a result of training, findings are less consistent when it comes to the far transfer effects. For example, some studies have replicated the findings of transfer to reasoning tasks (Jaeggi et al., 2008) whereas others have not found such effects (Holmes et al., 2009). It is at the moment not clear what underlies these differences in findings but potential explanations might be found in differences in sample characteristics such as age, clinical status and baseline capacity levels. Difficulties in improving reasoning ability by improving WM leads to the question whether reasoning ability instead can be directly trained via implicit directed training as has been described for WM. This is what we assessed first in typically developing children in Study II and then in a clinical sample of children with intellectual disabilities in Study III.

1.5.2.1.1 Effects of training in the brain.

The improvements resulting from WM training have been linked to increased activity in WM related areas of frontal and parietal cortices in both young adults (Olesen et al., 2004) and in children (D. D. Jolles, Grol, Van Buchem, Rombouts, & Crone, 2010), reflecting cortical plasticity assumed to be involved in these improvements. Jolles et al. (2012) have also demonstrated alterations in functional connectivity following training

in adults but not in children. A study focusing training on updating mechanisms identified striatal activity as a predictor of transfer effects and showed that transfer was limited to tasks that activates similar brain regions (Dahlin et al., 2008). Given the extensive evidence for an involvement of the dopaminergic system in WM functions it would be reasonable to hypothesise a role for dopamine in the effects. The idea would be that just as manipulation of dopamine levels in the brain can alter WM function, so might alterations of WM function through environmental influence affect the dopaminergic system in the brain. A method allowing for the investigation of the distribution of particular neurotransmitters *in vivo* in the human brain is positron emission tomography (PET). So far, two studies have used this method in order to map changes in the dopaminergic system following working memory training. The first study to investigate the topic used the Cogmed WM training programme as described above (McNab et al., 2009). Five weeks of training was related to significant alterations of dopamine D1 receptor density in parietal and frontal cortical areas measured at rest. Greater levels of improvements following training were generally related to a larger decrease in D1 receptor binding potential. The effects in this study were seen exclusively for D1 receptors in cortical areas with no effect observed for sub-cortical D2 receptor binding potential. An effect of striatal D2 binding potential was however observed in a second study investigating effects of a WM training programme focusing on updating mechanisms (Bäckman et al., 2011). This study differed from the McNab et al. in a number of aspects, most importantly the training programme, ligands used and acquisition of PET data. PET data was acquired during rest in the McNab et al. study and thus results reflect stable changes in dopamine receptor density. On the other hand Bäckman et al. compared binding potential for an active task performance minus control task performance contrast. Thus results are more related to task performance and could also reflect changes in strategies used when performing the task. Together these studies show that a relatively short period of positive environmental stimulation is sufficient to affect the activity and dopaminergic system in the brain.

1.5.3 Gene*environment interaction.

Data on intelligence measures from the last century have shown huge increases in performance within the western world. This phenomenon, named the Flynn effect after the researcher first to describe it, James Flynn, is at a first glance paradoxical considering the large heritability of intelligence as described above. How can a trait that has mainly genetic foundations change at a rate in which no substantial changes in the underlying genetic factors can be expected? One possible explanation for this, provided by Flynn and his colleague William Dickens, is the introduction of what they called multipliers (Dickens & Flynn, 2001). This idea suggests the occurrence of gene by environment interactions, in which the genes we are born with will influence our choice of environment throughout life. Having a small genetic predisposition that provides an advantage on a specific ability, say intelligence, might increase our internal and external motivation for activities that require this ability, which will allow us to develop this further. Thus a gene-by-environment interaction occurs that amplifies the effects of an initially small genetic factor. This is supported by the observation that genetic

effects on cognitive performance are enhanced throughout the life span, from around 30% in young children and up to 80% in older adults (Deary et al., 2010). Multiplier effects would then lead to genetic effects appearing large within samples where the environmental conditions are similar. However if there is a large difference in environmental conditions, such as those that have occurred in the western societies during the last century, this will have a large influence on the abilities of all individuals in that sample, thus providing an explanation for the rise of intelligence across time in the western world. This suggests that a traditional discussion of whether genes or environment are of greatest importance are particular difficult to carry out. Rather, it shows that they are both of importance and that they do not act in isolation but rather in interaction with each other.

Another way that gene by environment interactions can occur is that genes can influence the degree to which we are affected by the environment. This has traditionally been considered in the light of "vulnerability genes"; that carriers of certain genetic variants will be more sensitive to negative life events. One example is the observation that carriers of the short alleles of the 5-HTT polymorphism (located in the serotonin transporter gene, *SLC64A*) are more vulnerable to stressful life events, resulting in more depressive symptoms and higher risk of suicidality (Caspi & Moffitt, 2006).

Belsky and others (Belsky et al., 2009) have suggested that the idea of "vulnerability genes" should be rephrased to consider "plasticity genes", as rather than making us more vulnerable, some genetic variants might influence our brains to be more plastic and subsequently more susceptible to environmental influences for better or worse. This would suggest that carriers of these genetic variants might be more vulnerable to negative environmental influences, but similarly might benefit more from a positive environment. This is supported by observations that dopaminergic related genes show this pattern of effects on self-regulation as a result of parenting quality (Belsky & Beaver,2011).

*1.5.3.1 Training as a method of studying gene*environment interactions*

The interaction between genes and environment poses a problem for correlational studies such as large epidemiological studies. If genes influence our selection of environment it will be difficult to completely distinguish genetic effects from environmental effects. One solution around this is to carry out traditional randomised controlled trials in which the environment is manipulated in a controlled manner. By using this method we can control for the effects of both environment (exposure or no exposure) and genetic effects (influence from different genetic variations). This is what we did in Study IV, using cognitive training as a positive environmental manipulation.

2 AIMS AND HYPOTHESES

2.1 STUDY I

The aim of Study I was to assess the association of certain candidate genes on WM capacity during childhood and early adulthood. In addition, we aimed to assess the effect on brain activity and structure of any behaviourally associated genotype. We hypothesised that polymorphisms within genes previously associated with learning and memory, or ADHD, would be associated with WM capacity as well as brain function and structure.

2.2 STUDY II

The aim of Study II was to develop and assess a training programme consisting of NVR and WM tasks. We hypothesised that 1) training on NVR reasoning tasks would lead to improvements on a measure of *Gf*, 2) training on WM would lead to improvements on non-trained measures of WM, 3) that training on either construct (either WM or NVR) would transfer to improvements within the other construct 4) that training a combination of the two tasks would lead to additional synergistic effects.

2.3 STUDY III

Study III aimed at assessing the feasibility of training on the programme developed in study II in a group of children with intellectual disability. In addition we aimed to assess transfer effects of such training and to understand what factors predict training progress. We hypothesised that children with intellectual disability would benefit from training on NVR and WM tasks and that this would lead to improved performance on non-trained measures of NVR and WM.

2.4 STUDY IV

Study IV aimed to assess the effects of candidate genes involved in the dopaminergic system on transfer effects following WM and NVR training. We hypothesised that genetic variants influencing dopamine levels in the brain would be associated with the level of improvement observed following training.

3 METHODS

3.1 PARTICIPANTS

Study I included participants from the Brain Child sample, a randomly selected community sample of children and young adults aged 6 to 25 years. This sample was randomly selected and contacted using the population registry in order to provide a representative sample of Swedish children and young adults. Participants with a psychiatric diagnosis other than ADHD or dyslexia were excluded.

Studies I, II and IV included a sample of typically developing children between 4 and 4.5 years. These children were recruited from the Stockholm area through advertisements in local newspapers, preschools and on the Developmental Cognitive Neuroscience Laboratory webpage.

Participants in Study III were patients with intellectual disability, registered with the health care system in the area of Buskerud in Norway. Children with a chronological age of 6-12 years with intellectual disability were included. Exclusion criteria were a diagnosis of autism or motor or sensory problems that were judged to affect practical training ability. For practical reasons children with guardians requiring an interpreter for conversations in Norwegian were also excluded.

In all studies participants and legal guardians for children gave informed consent before participation. All studies were approved by the local ethics committee.

3.2 SELECTION OF CANDIDATE GENES

Candidate genes for Study I were selected based on previous literature on genes associated with either specific cognitive functions such as learning and memory or with the diagnoses of ADHD in which deficits of such functions are important symptoms (Gizer, Ficks, & Waldman, 2009). The selection of genes previously associated with ADHD is based on the idea of WM being an intermediate factor, a so-called endophenotype for ADHD (Castellanos & Tannock, 2002). This idea suggests that a disadvantageous genetic polymorphism will (through an effect on brain function) impair WM capacity, which in turn will contribute to the behavioural symptoms of ADHD. Our hypothesis was therefore that some of the previously found associations observed for candidate genes and ADHD might in fact reflect an association between these genes and WM (and brain function).

In total 55 single nucleotide polymorphisms (SNPs) located in 18 different genes were analysed in the large Brain Child community sample. For Study IV, a subsample of SNPs associated with dopaminergic function were selected for analyses in the sample of 4-year-olds. In Study I, data from the sample of 4-year-olds was included for the rs363039 polymorphism in the *SNAP25* gene.

3.3 GENETIC ANALYSES

For studies I and IV saliva and/or blood samples were collected for extraction of genomic DNA (deoxyribonucleic acid). The genetic information contained within DNA is determined by the sequence and combination of four different nucleotide bases: adenine (A), thymine (T), cytosine (C) and guanine (G); which in the double strand helix of the DNA conformation, are normally paired together: A with T and G with C. DNA was analysed at a number of places along the molecule, in the genes of interests, by genotyping using matrix-assisted laser desorption/ionisation time of flight mass spectrometry. This method allows for looking at the level of single base, at so-called SNPs. One SNP is a base which can differ between individuals and/or chromosomes. As each chromosome exists in two copies (except for the X and Y chromosomes in males, which only exist in one version), each gene or section of DNA will exist in two versions in all cells (except the gametes) of any one individual. Considering bases at one specific position in both chromosomes, therefore allows three possible combinations (genotypes) in any individual. For example, when a position has either an "A" or a "G" base, if an individual has two copies of the "A" (called the "A" allele), he/she is homozygote AA, if he/she has two copies of the G allele, then he/she is homozygote GG; and when he/she has one copy of each allele, then he/she is heterozygote AG.

We based our choice of SNPs on previous literature reporting associations with the phenotypes of interest (ADHD, learning and memory). We also took into account their correlation to other SNPs (for example linkage disequilibrium), so that an as large portion as possible of the gene would be covered. In addition, we checked frequency of the less frequent allele (so-called minor allele frequency) to increase our chances for having a representation of all genotypes at that marker in our sample set.

3.4 MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) is a commonly used method allowing for *in-vivo* imaging of structure and function of the human brain. Compared to other imaging techniques, MRI has its major benefits in being non-invasive and there are no known side effects associated with the method. It also has an advantage of providing a relatively good spatial resolution (with voxel size often around 1*1*1mm). As the name suggests, the method is based on interactions between magnetic field and its effects on protons in the water molecules of our body tissues. The MRI scanner induces a strong magnetic field, usually 1.5 or 3 Tesla, and when a person is placed in the scanner the protons in their body will align according to the direction of the applied magnetic field. A second manipulation is then added with a pulse of radio frequency leading to an alternate electromagnetic field. This will excite the protons making them switch alignment from the previous low energy state to a higher energy state. After the radio frequency pulse has terminated the protons will return to the original low energy state and this will be coupled with an exchange of energy that can be measured using special receiver coils that are placed around the body part of interest. Different tissues

within the brain (and rest of the body) have different proton densities and this will lead to slightly different signals received by the coils. These differences in signals are then transformed into three-dimensional images in which different tissues can be distinguished.

These images are then processed in a number of steps before statistical analyses can be performed, including correcting for motion that occurred during data acquisition, normalisation of brain structure to a template in order to correct for large structural differences, and smoothing of the data in order to reduce noise.

3.4.1 Voxel based morphometry

One type of analyses that can be used in order to compare concentration of grey matter between groups is called voxel based morphometry (VBM). This method allows whole brain segmentation into grey matter, white matter and cerebral spinal fluid. The method assumes only one type of tissue in each voxel and analyses are performed on a voxel-by-voxel basis on a group level. The output is the density, or concentration, of grey matter in that voxel over the whole group being analysed (and can thus take a value between 0 and 1). Performing these analyses for different comparison groups (for example groups with different genetic variations as was done in Study I) on a whole brain level can thus identify local and global structural differences between groups.

3.4.2 Functional Magnetic Resonance Imaging

Another utilisation of the MRI technique is functional MRI (fMRI), which serves as proxy for measuring brain activity. This technique measure what is called the blood-oxygen-dependent (BOLD) signal, which is based on the difference in magnetic properties between oxygen rich (oxygenated) and oxygen poor (deoxygenated) blood. Deoxygenated blood has a higher degree of magnetisms and therefore disturbs the signal MR to a larger extent. Consequently an increase in oxygenated blood will result in a stronger MR signal. As an increase of blood flow and following increase in oxygenated blood is believed to be related to increased neural activity, the BOLD signal is interpreted as an indirect measure of neural activity in a certain brain area.

In order to be able to link neural activity to an isolated behavioural task it is necessary to compare the BOLD signal during task performance with BOLD signal measured when the participant is performing some similar task, that importantly, lacks the cognitive component that is being investigated. In Study I participants therefore performed both a visuo spatial WM task (similar to the visuo-spatial grid task described below) and a control task that was matched to the WM task as close as possible regarding visual stimuli and response mode but without requiring a substantial demand on WM. A contrast of BOLD signal during the WM task with the BOLD signal during the control was then created to represent activity directly related to the WM processes.

3.5 COGNITIVE ASSESSMENTS

3.5.1 Working memory

To measure visuo-spatial WM all studies used a computerised visuo-spatial grid task, which requires memorising the spatial location and temporal sequence of presented stimuli. A 4*4 grid is displayed on the computer screen and dots are displayed in the squares in a sequential order (figure 4). The participant is then asked to point to the squares in the same order that the dots were displayed. The task is a span task that is terminated after a certain number of incorrect answers on one level (where level equals number of items to be remembered). Studies I and III used the grid task from the Automated Working Memory Assessment (Alloway, 2007). Study II and IV used a version of the grid task that was previously developed in the Klingberg lab (Bergman Nutley, Söderqvist, Bryde, Humphreys, & Klingberg, 2010).

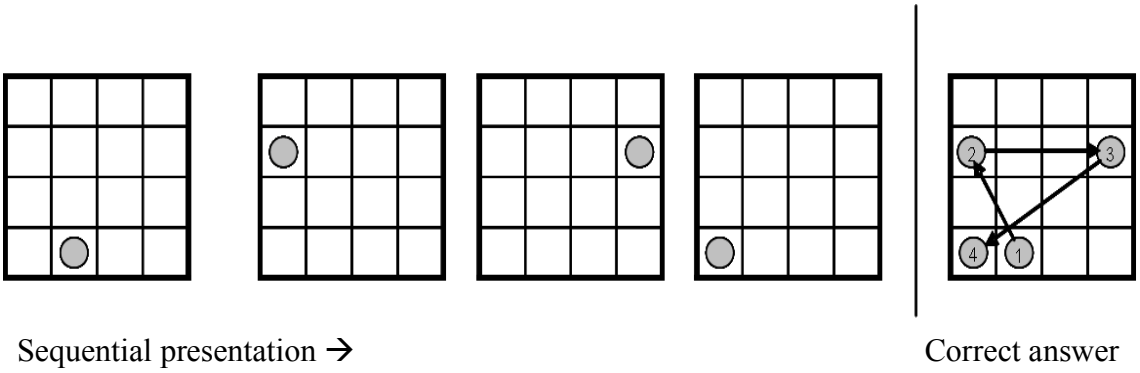

Figure 4. A schematic example of a visuo-spatial grid task.

Studies II, III and IV also used a visuo-spatial WM task with an added processing component, the Odd One Out task from the Automated Working Memory Assessment (Alloway, 2007). In this task, a set of three figures is displayed on a computer screen. The first requirement is for the participant to point to the figure that differs from the other two, the odd one out. Second, a set of three empty squares is displayed and the participant is asked to point to the empty square that previously contained the odd one out figure. Level of difficulty (number of sets displayed and number of odd one out figures to remember) is successively increased until the participant has performed three incorrect answers on one level, which leads to termination of the task.

Two different WM tasks within the verbal domain were used. All studies used digit (Study I) or word (Studies II, III, and IV) span tasks. These tasks consist of items (either digits or words) that are read aloud to the participant who has to repeat these in either the same order that they were read aloud (forward condition) or in the backwards order (backwards condition). The number of items starts with two and increases with level of difficulty. This task terminates after the participant has made a set number of incorrect answers.

In Study I, a verbal three-back task was used. This task places a high demand on an updating mechanism which is suggested to be an important function of WM. The tasks consists of a number of words that are read aloud to the participant and for each word the participant has to decide on whether that word is the same as the word that was presented three words back in the list. A score was calculated based on hits (correct "yes" answers) minus false alarms (incorrect "yes" answers), which was used in analyses.

3.5.2 Reasoning ability

To measure reasoning ability three different tests were used: the Raven's progressive matrices (Raven, 1998), Block design from Wechsler Preeschool and Primary Scale of Intelligence (WPPSI) (Wechsler, 2004), and three sub-tests from the Leiter Test Battery: Repeated Patterns, Sequential Order and Classifications (Roid & Miller, 1997).

In Raven's progressive matrices the participant is shown an incomplete matrix. Within each matrix a serial change in stimuli occurs that needs to be identified in order to complete the matrix. Participants choose one out of six alternative response options. This test assesses the ability to identify relationships and infer rules and it loads highly on *Gf*.

In studies II, III and IV the Block Design task from WPPSI (Wechsler, 2004) was used. This task is a measure of non-verbal, or perceptual, reasoning. In this task, the participant is given red-and-white coloured blocks and is asked to use these in order to replicate a certain displayed pattern. It thus requires analysing and synthesising abstract visual stimuli. Unlike the other reasoning tasks used, the Block Design is a timed task with scoring being dependent on not only accuracy but also how quickly the participant replicate each design.

3.5.3 Attention

In studies II and III we included the Auditory Attention task from the NEPSY test battery (Brooks, Sherman, & Strauss, 2009). This task assesses the child's ability to selectively attain to auditory stimuli and to sustain this attention. The task consists of a number of pre-recorded words that are being read aloud at one word per second. The child has to respond to a certain target word (the word "red") by placing a red foam figure in a box. Scores are awarded for each correct response within a certain time limit (maximum of two seconds), whilst scores are withdrawn for incorrect responses (responding to a word other than the target word).

3.6 WORKING MEMORY TRAINING

Studies II, III and IV used the WM training programme developed by Cogmed Systems, Cogmed JM. This training programme is developed to be suitable for young children or other individuals who are not fully confident with numbers and letters. It includes seven different WM tasks. The tasks consist of figures called Munchers that are located in different settings (e.g., on a roller-coaster, or in a swimming pool, see figure 5 for examples). Some of the Munchers will, in a sequential order, briefly change colour and make a sound ("laugh") and the task is to remember which Munchers changed colour and "laughed" and in which order this occurred. All tasks in this training programme are within the visuo-spatial domain. The choice to use this programme was motivated by suggestions that spatial spatial storage have stronger correlation to *Gf* than verbal storage (Kane et al., 2004). Furthermore, including only visuo-spatial tasks reduced the potential risk of influence from other factors of cognitive development such as digit and letter awareness, something of particular importance when working with young and clinical samples. This training programme employs an algorithm that controls level of difficulty (number of items to be remembered) based on the participants' performance. This algorithm is an important feature as it provides training that is close to the highest capacity of the participant, and thus provides constant challenge.

Figure 5. Some examples from the Cogmed JM training programme.

3.7 DEVELOPMENT OF NON-VERBAL REASONING TRAINING PROGRAMME

Tasks for the NVR training programme were developed based on three subsets of the Leiter Test Battery (Roid & Miller, 1997). The three subsets that have the highest load on *Gf* in the younger age groups (Repeated Pattern, Classifications, and Sequential Order) were chosen for this purpose. All tasks were developed to be computerised and consisted of a set of cards with geometrical figures that could be altered in a number of different parameters such as shape, colour and size. For each task, some card slots were empty and the task was to fill these with target cards. For Repeated Patterns, a series of cards were displayed that together formed a pattern, such as an alternation in colour, and the task was to complete this pattern choosing from a set of answer cards. In Sequential Order a series of cards were displayed that together formed a sequence, for example figures that became smaller and smaller for each card. Just like in Repeated Patterns, the task was to complete this sequence choosing from a set of answer cards. In Classifications a set of cards was displayed, each card with an empty box below it. The task was to place answer cards in the correct empty boxes, based on matching the items on some parameter such as matching colour or matching shape. For all subtests the parameters of which decision should be made were randomised for each trial.

After having designed a large number of items, these were assessed in a sample (N = 17) of 4-year-old children in order to map their level of difficulty. A Rasch analyses was performed to create a ranking of the items' difficulty. However, this ranking only told us about the general difficulty of these items and did not allow us to judge why they were difficult. For the training to be efficient, the increase in difficulty naturally needs to be based on an increased difficulty on the NVR aspect of the task and not reflect an increase on some other cognitive or perceptual demand. We therefore compared how different items were predicted by performance on NVR tasks (the original three subtests from the Leiter Test Battery, and Block Design from WPPSI), and on a WM task (Viuso-spatial Grid task). This was done using backwards logistic regression analyses with the probability of passing an item used as the dependent variable. As independent variables we included the load on different rules (e.g. number of distracters), a composite of the NVR scores, WM performance, interaction terms between NVR and WM scores and all different rules and age. The different rules that tasks could have included number of distracter cards, number of cards and length of a pattern as well as number of open slots to be filled. This analysis allowed us to identify rules that were most affected by NVR performance (as indicated by the NVR interaction) and thus this allowed us to conclude that increasing difficulty based on these rules would tap an increased demand for NVR capacity. Based on these findings we created a new hierarchy of items that was tested in a second pilot study including 12 6-year-olds. Based on the results from this we performed a second Rasch analyses which guided us in the design of the final training programme. The NVR training employed a similar algorithm for adjustment of difficulty levels as described for the WM training programme above.

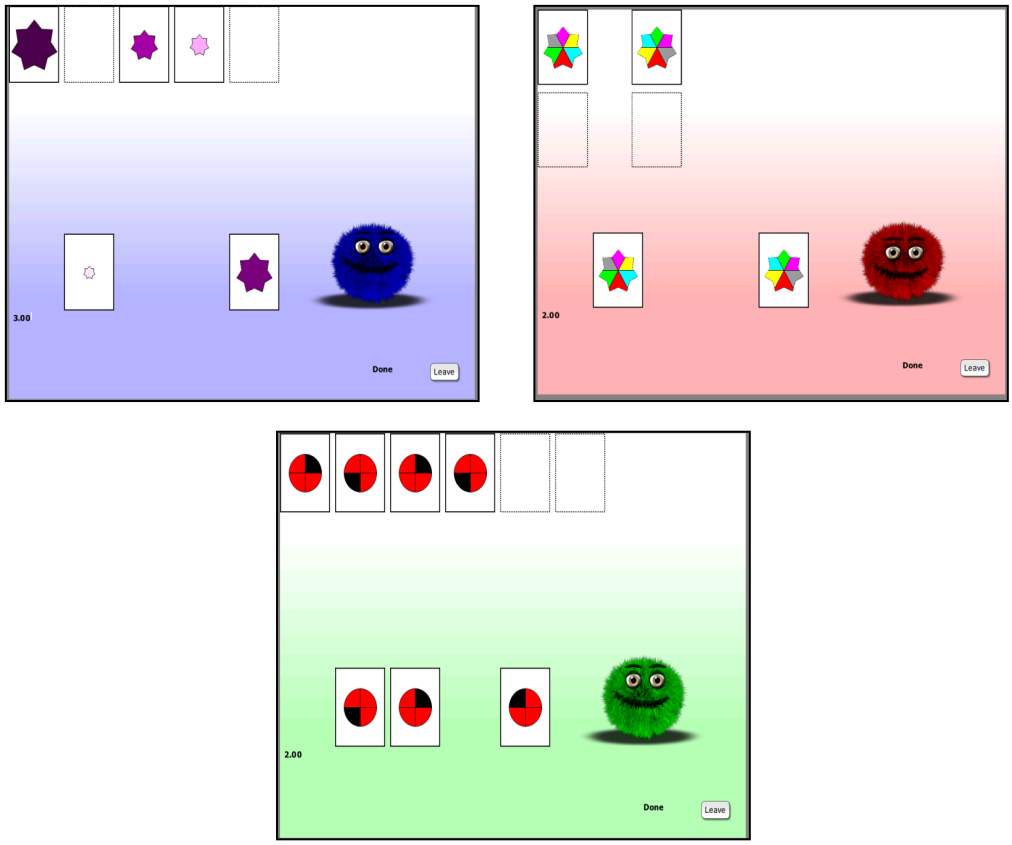

Figure 6. Examples of tasks included in the NVR training, Sequential Order with blue background, Classifications with red background, and Repeated Pattern with green background.

3.8 NON-ADAPTIVE TRAINING

In all training studies (II, III, and IV) we used a non-adaptive training programme as control training. These programmes contained the same tasks as the adaptive versions described above but with the difference that the difficulty was always kept to the easiest levels. This allows for a strict control for the effects of other aspects that follow with the training such as one-on-one interaction with an adult and regularly sitting down and focusing on a specific task for a relatively long period of time. In addition, both participants and test administers were blind to group membership and therefore we believe that we also controlled for effects associated with expectancy.

3.9 TRAINING PROCEDURE

For studies II, III and IV training took place in the home with parents supervising the training (or in some cases in Study III, the training took place in the child's school with teachers' supervising the training). Parents and teachers were given oral and written instructions on how to supervise the training and what kind of feedback they were allowed to give the children. These instructions included giving encouraging feedback when the child answered correctly and encouraging the child to pay attention when a mistake was made (and the programme corrected that mistake), but to never help the child choose which answer to make. In addition to this supervision, researchers

involved in the study followed the training progress via a web-based server. This allowed us to control the time spent training and also to give individual feedback to the participants. Such feedback was given by e-mail or phone calls once a week. Training in Studies II and IV was carried out for approximately 15 minutes a day, for five days a week for five weeks. The set up was the same for Study III with the exception that training was performed for approximately 20 minutes a day. A minimum of 20 finished training sessions was required for the inclusion of a participant in the analyses.

4 RESULTS

4.1 STUDY I

4.1.1 Behavioural association

We assessed 55 SNPs in a sample of 330 children and young adults. Based on performances on three WM tasks (a visuo-spatial grid task, a backwards digit recall task, and a verbal three-back task) we created a latent variable representing WM capacity for each individual. This latent variable represents the shared variance between these three tasks and is taken to represent WM capacity. This approach reduces task specific variance and variance occurring from random noise.

Results revealed a significant association between one SNP, rs363039, and WM capacity. This SNP is located within the gene coding for the synaptosomal-associated protein at 25kDa (*SNAP25*). We found the A-allele of this genotype to be associated with superior WM capacity. Post-hoc assessment showed that a strong association with the visuo-spatial grid task explained this association (figure 7). In addition, we found significant associations to measures of fluid reasoning (Raven's progressive matrices), processing speed and reading ability. The A-allele was associated with superior performance on all tasks.

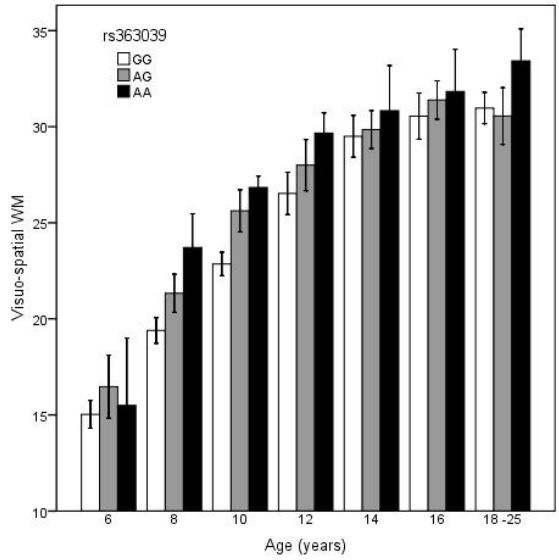

Figure 7. Effect of the rs363039 polymorphism on performance on a visuo-spatial WM task across age groups (error bars representing standard error of mean).

In order to replicate these findings we analysed the association of this same SNP and WM performance in 88 4-year-old children. In this sample we found an association with a slightly larger effect size and, replicating the effects in the larger sample, the A-allele was found to be a predictor of superior performance on a visuo-spatial working memory task.

4.1.2 Association with brain activity and structure

The behavioural findings guided us in further investigations of the rs363039 polymorphism on brain structure and activity in a subsample of the larger community sample. We used VBM in order to assess grey matter density and fMRI as an estimate of brain activity. VBM analyses showed an association between the polymorphism and grey matter density in the posterior cingulate cortex (PCC) (Figure 8A). This association was dependent on age as is demonstrated in figure 8B) Whole brain analyses of WM dependent activity showed an association with the polymorphism to activity in an area of the PCC, overlapping with the area for which effects on grey matter was found (figure 8C). This area shows 'deactivation' during performance of the WM task, meaning that the activity is larger during the control (low cognitive load) task compared with the WM (high cognitive load) task. This difference followed a dosage effect with larger deactivation associated with increasing A-alleles as can be seen in figure 8D.

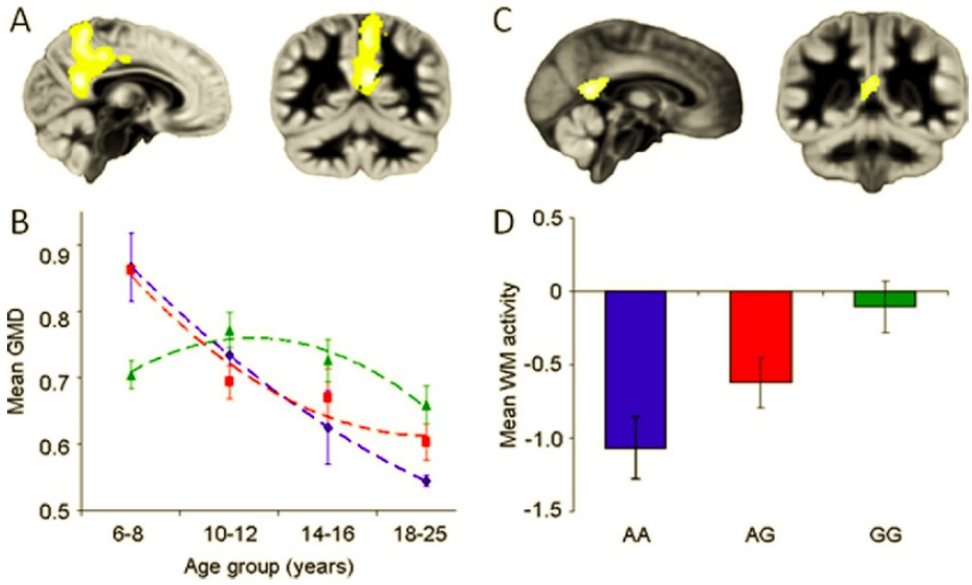

Figure 8. Effect of the rs363039 polymorphism on brain structure and function. A shows the area within the PCC where *SNAP25* genotype predicted grey matter density (GMD). These effects are plotted in B genotype colour coded, AA= blue, AG = red, GG = green. C and D illustrate the effects of genotype on WM related activity within the PCC.

4.1.3 Preliminary data

4.1.3.1 Follow-up

The sample included in Study I has been followed up twice, once after two years (T2), and once after four years (in which only the subsample included in the imaging sample was included). Mixed model analyses measuring the development over time revealed a significant main effect of genotype (p = 0.034), time*genotype interaction (p < 0.001), and a time*age*genotype interaction (p = 0.002). In addition significant effects of time (p <0.001), age (p < 0.001), and time*age (p <0.001) were observed. There was no

significant interaction between genotype and age. Effect of genotype over time is illustrated in figure 9.

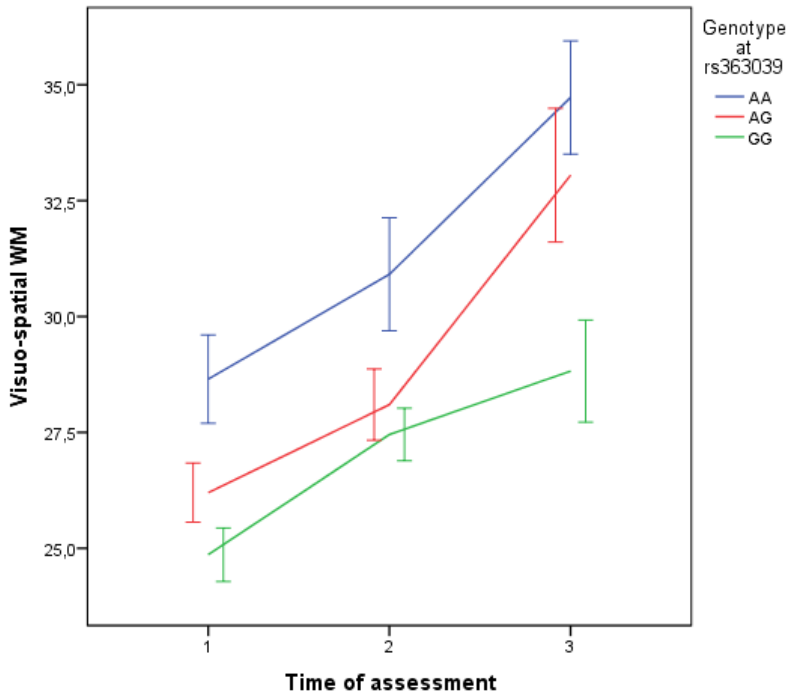

Figure 9. Effects of *SNAP25* genotype on performance on a visuo-spatial WM task at three time points. Bars represent standard error of mean.

4.1.3.2 Association with ADHD symptoms

After publication of Study I, we have performed additional analyses looking at the association with the rs363039 polymorphism and ADHD symptoms within the large Brain Child sample examined in Study I. Measures of ADHD symptoms were collected from three different questionnaires. First we used the diagnostic items for ADHD from DSM-IV (American Psychiatric & American Psychiatric Association. Task Force on, 2000) completed by both the parents and teacher for each child. In addition the parents also filled out the Child Behaviour Checklist (CBCL) questionnaire from which we used the scores of ADHD symptoms. From these three measures we created a latent variable that we used as a measure of each individual's degree of ADHD related symptoms. As ADHD is more prevalent amongst males we controlled for gender effects in these analyses. Multiple regression analyses using the latent ADHD measure as a dependent variable and rs363039, gender, rs363039*gender, and age as independent variables, revealed a significant effect of genotype ($\beta = 0.291$, $p = 0.014$), as well as a trend effect for a genotype*gender interaction ($\beta = -0.338$, $p = 0.065$). Gender and age did not significantly predict ADHD symptoms. Performing these analyses for the two genders separated shows that the effect of the *SNAP25* genotype influences ADHD symptoms in males only ($p = 0.025$, compared to $p = 0.667$ for females). In the group of males, carriers of the G-allele had on average higher scores (more) for ADHD symptoms. This observation fits well with the results in Study I

where the G-allele was associated with poorer WM capacity. This difference is illustrated in figure 10.

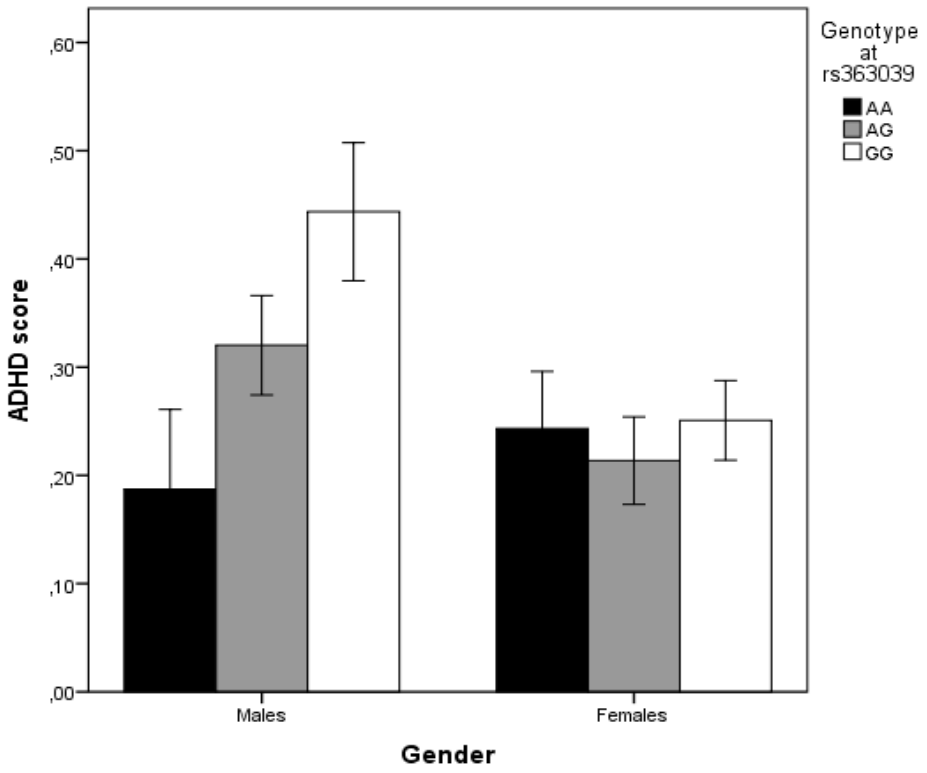

Figure 10. Effects of the rs363039 genotype on ADHD symptoms at T1 for the two genders separated. Error bars represent standard error of the mean.

We further investigated if the effects of the genotype on ADHD symptoms could be explained through its effects on WM capacity by including WM capacity in the regression model above. This was not found to be the case as both the genotype and genotype*gender remained significantly contributing to ADHD scores ($\beta = 0.266$, $p = 0.021$, and $\beta = -0.354$, $p = 0.047$ respectively) after controlling for the significant contribution of WM and age ($\beta = -0.369$, $p = 0.001$, and $\beta = 0.220$, $p = 0.041$ respectively).

Following these findings we investigated if the degree of ADHD symptoms also relate to activity within the PCC, as was shown for the genotype. This was found to be the case for both males ($r = 0.474$, $p = 0.040$) and females ($r = 0.532$, $p = 0.011$) (correlation for the gender groups combined: $r = 0.494$, $p = 0.001$) with higher scores on ADHD symptoms being associated with higher level of activity in the PCC during the WM task. Furthermore, the activity in PCC measured at time point one (T1) significantly predicted ADHD symptoms two years later at T2 ($r = 0.398$, $p = 0.002$ (figure 11).

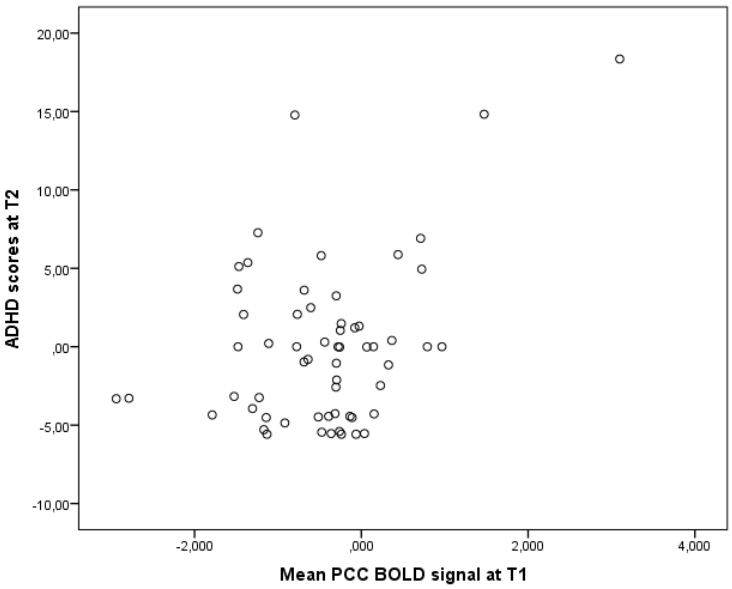

Figure 11. Correlation between WM related activity within the PCC measured at T1 and ADHD scores measured at T2.

There was no significant effect of genotype or genotype-by-gender interaction on ADHD scores at T2.

4.2 STUDY II

The main finding of this study is that it is possible to train NVR and that this training leads to significant improvements on a latent variable measuring *Gf*. We found that approximately 15 minutes of training during 25 sessions was sufficient for preschool aged children to significantly improve their cognitive performance. Furthermore, children training on NVR tasks not only improved on a measure of *Gf*, but also showed a trend for transfer between cognitive constructs as they improved on a visuo-spatial WM task. Children training on WM tasks significantly improved their performance on other WM tasks that were dissimilar to those trained on. Training on WM did however not show significant transfer to measures on *Gf* in this sample. We also analysed possible synergistic effects of training a combination of both WM and NVR, measured as an interaction effect between WM and NVR training. This was only found to have an effect for the two tasks that were very similar to those being trained (Leiter tasks and visuo-spatial grid task). Results are summarised in figure 12.

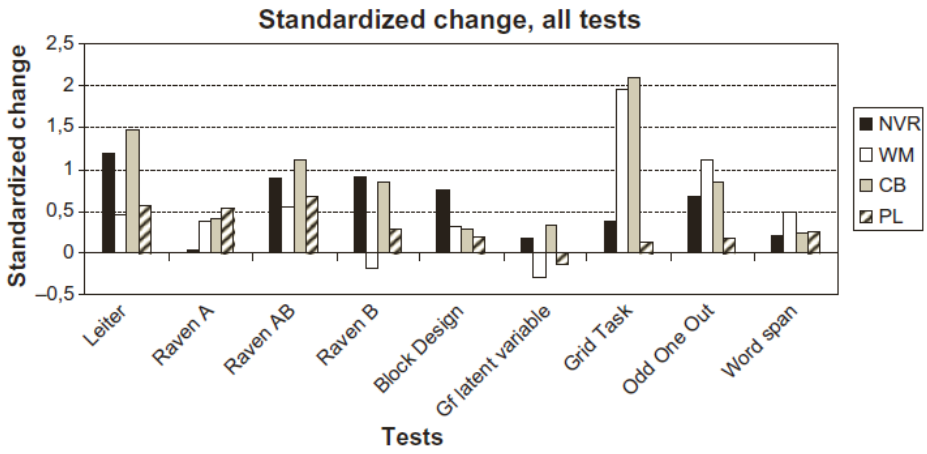

Figure 12. Improvements in cognitive measures following WM and NVR training.

4.3 STUDY III

In study III we found that children with intellectual disability can benefit from cognitive training as described in study II. However, these findings show large variance in training progress, that is how much a child improved during training as illustrated in figure 13.

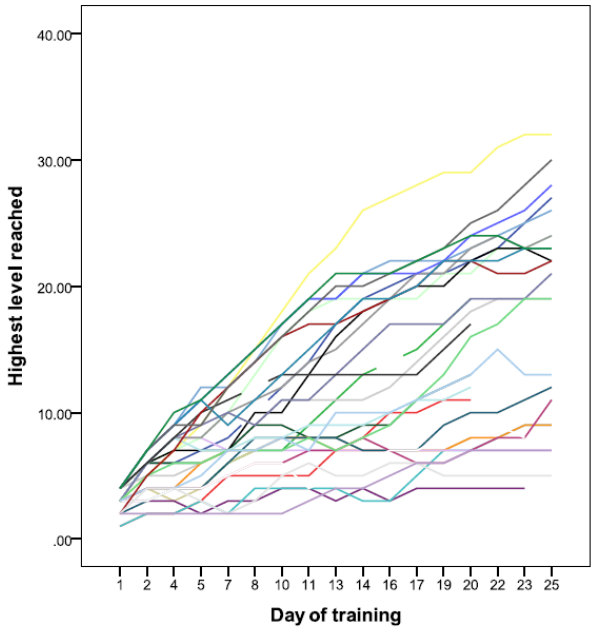

Figure 13. Progress on a NVR task during training. Each line represents one participant.

Furthermore, whereas we did find trend effects of training on both measures of WM, a measure of NVR, and language comprehension, these effects were significantly predicted by amount of progress achieved during training (table 1). We found that those children that improved most on the trained tasks were also those that showed the largest transfer to measures of WM, NVR, and language comprehension. For language comprehension and Block Design, gender significantly interacted with the training effect: females gained more on language comprehension as a result of training, whereas

males gained more on the Block Design as a result of training. We were also able to predict factors influencing the training progress. A larger progress during training was related to higher levels of performance on cognitive tasks observed prior to training, especially performance on word span backwards. Absence of co-morbid diagnosis and being female was also associated with a greater training progress suggesting inter-individual differences in the capacity to improve performance during training. We performed a follow-up assessment with the same tests one year after training was completed. At this follow-up no significant effects of training were observed.

Outcome measure	**Variables**	**Standardised Beta**	**p-value**
Word span backwards	T1 Performance	0.679	<0.001
	Training	**0.293**	**0.009**
Word span forwards	T1 Performance	0.758	<0.001
Odd One Out	T1 Performance	0.789	<0.001
	Training	**0.241**	**0.010**
Block Design	T1 Performance	0.705	0.001
	Gender	-0.283	0.013
	Training	**0.323**	**0.042**
	Training*Gender	-0.279	0.079
Instructions	T1 Performance	0.795	<0.001
	Training*Gender	0.196	0.032
Auditory attention	T1 Performance	0.885	<0.001
Raven's	Gender	-0.226	0.071
	Age	0.271	0.096
	T1 performance	0.458	0.007

Table 1. The effect of training progress on transfer effects. Values in bold indicate stronger contribution of the training variable compared to the group variable.

4.4 STUDY IV

In Study IV we found that three SNPs (rs3863145, rs27072 , and rs40184), all located within the *DAT1* gene, were significantly associated with improvement on transfer tasks following the cognitive training performed in Study II. Two of these SNPs were associated with improvements on the latent variable measuring *Gf* and the third was associated with improvements on measures of WM. These SNPs were not significantly associated with baseline capacity, suggesting that they influence the degree of plasticity induced by cognitive training.

5 DISCUSSION

5.1 STUDY I – THE EFFECTS OF SNAP25 ON COGNITIVE PERFORMANCE AND BRAIN MATURATION

We identified an association between a polymorphism (rs363039) within the *SNAP25* gene and WM capacity. The *SNAP25* gene codes for a protein, with the same name (typically written as SNAP-25), that is a presynaptic plasma membrane of the SNARE protein family (Bark, Hahn, Ryabinin, & Wilson, 1995). Being located on the presynaptic membrane, it plays a crucial role in the binding of synaptic vesicles to this membrane allowing for exocytosis, the release of neurotransmitters contained within the vesicles into the synaptic cleft.

We also found that the same polymorphism within the *SNAP25* gene was associated with brain structure and brain function. The effects were located within the PCC, which has been suggested to be an important connecting area, a hub, in the so-called default mode network (DMN) (Fransson & Marrelec, 2008). By assessing how activity within different areas of the brain correlate one can measure what is called functional connectivity, and different networks of areas that are functionally connected appear in response to different activities. The DMN represents a network that shows increased activity when the participant is at rest and not performing a cognitively demanding task (Buckner, Andrews-Hanna, & Schacter, 2008; Fransson, 2005; Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001). Therefore, when measuring activity during a cognitively demanding task contrasted to a control task, a pattern of deactivation or lower level of activity will be observed in these related areas. The PCC is considered a hub in this DMN as it is most strongly connected to other areas within this network. Activity of this area has been related to lapses in attention and a larger degree of deactivation has been linked to higher cognitive performance (Sambataro et al., 2010; Weissman, Roberts, Visscher, & Woldorff, 2006). The latter was also observed in our sample, with a significant correlation between degree of deactivation and performance on a WM task outside the scanner.

The *SNAP25* polymorphism also affected gray matter density. As apparent in figure 8, from the older childhood years A-allele was associated with generally lower levels of grey matter density. The GG homozygotes on the other hand showed an initial increase of grey matter over age groups, which did not change direction with until adolescence. This could suggest that the GG homozygotes show a delayed developmental pattern, with the peak in grey matter density reached at an older age, something that has also been observed for children with ADHD (Shaw et al., 2007). In order to be able to make claims regarding development this should be investigated using data from the two follow-up assessments collected from this sample, however, at the time of writing this thesis these analyses were not yet completed.

Something that makes our results of particular relevance is that altered activation of the DMN has been identified in children with ADHD. This adds a step in which *SNAP25* might influence ADHD symptomology. By affecting activity in the PCC, WM capacity and other cognitive functioning might be influenced, which in turn might give rise to some of the characteristic symptoms in ADHD. This is consistent with the default-mode interference hypothesis proposed by Edmund Sonuga-Barke and Xavier Castellanos (Sonuga-Barke & Castellanos, 2007), in which a failure to consistently decrease activity in the DMN during task performance will interfere with task specific neural activity, resulting in impairments in performance. The associations found in in previous literature, in Study I and in the preliminary analyses presented in this thesis are illustrated in figure 14.

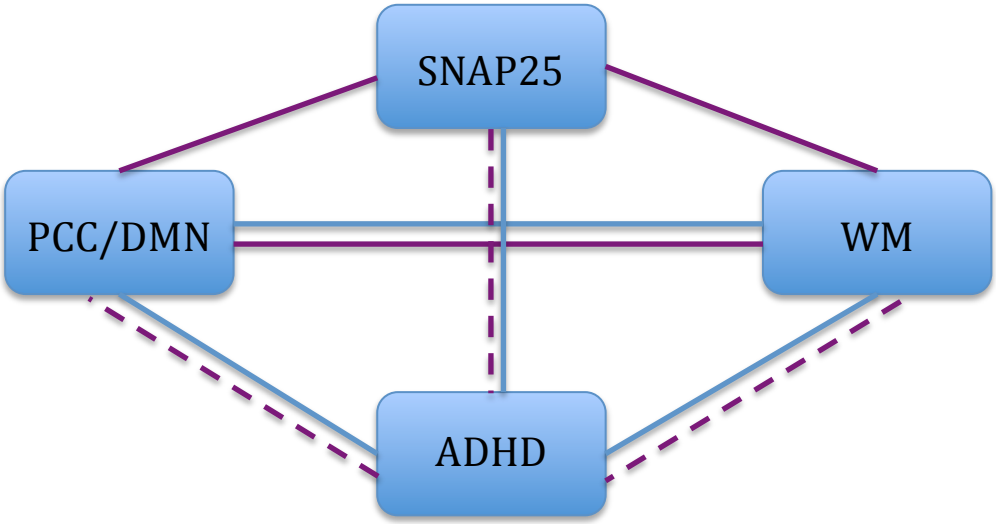

Figure 14. Illustration of associations between *SNAP25*, WM, ADHD, and DMN. Associations from previous literature are illustrated with blue lines, associations from Study I are illustrated with purple solid lines, and preliminary findings reported in this thesis are illustrated with purple dashed lines.

5.1.1 Association with ADHD symptoms in a typically developing sample

Novel analyses revealed that genotype in *SNAP25* significantly predict ADHD symptoms, particularly in males. This fits well with previous literature repeatedly showing association between *SNAP25* and ADHD (Faraone et al., 2005; Gizer et al., 2009). Our study is different in that we are not comparing patients with ADHD with a typically developing sample, rather our results show that *SNAP25* also influences ADHD symptoms that are within a normal distribution. Controlling for the effect of *SNAP25* on WM capacity did not explain this association, suggesting that *SNAP25* genotype explains some variance in ADHD symptoms that is beyond its effect on WM capacity.

ADHD scores were also significantly related to activity in the PCC, with higher levels of activity predicting higher ratings on the ADHD scales. This fits well with previous

literature linking activity in the PCC to lapses in attention (Weissman et al., 2006) and altered patterns of activation within the DMN in children with ADHD (Fair et al., 2010; Tomasi & Volkow, 2012).

Finally, we used measures at T1 in order to predict ADHD symptoms two years later. Interestingly, we found that activity within the PCC at T1 significantly correlated with ADHD symptoms at T2. More surprisingly, the effect of genotype was no longer significant at T2.

5.1.1.1 Gender differences

We observed a significant gender interaction with the genotype for predicting T1 ADHD symptoms, with effects seen for males only. Gender differences have previously been observed for SNAP-25 density in post-mortem brains of both healthy elderly controls and adults with Down's syndrome (Downes et al., 2008). Animal studies have also revealed gender differences in SNAP-25 expression in rat cortex during development, with male rats showing higher levels of expression. These differences were erased after neonatal treatment with either oestrogens or testosterone (Lustig, Hua, Wilson, & Federoff, 1993). These findings have lead to the suggestions that *SNAP25* can potentially be underlying (some of) the gender differences seen for ADHD (Ghezzo et al., 2009). Finally, gender differences have recently been demonstrated for the effect of the rs363039 polymorphism in humans (Cagliani et al., 2012). In this study the genotype was associated with verbal performance in girls aged 3-11 years (with heterozygotes showing superior performance), but no significant effects were seen for males.

Thus our findings of gender differences have some support from previous literature. It is however not clear why genotype interacts with gender only for the ADHD symptoms and not the cognitive measures or brain activity. Nor is it clear why we see effects in males and not females, as the opposite pattern was previously observed for cognitive performance (Cagliani et al., 2012). Although the evidence above suggests a biological explanation for the gender effects, one other potential underlying explanation is that ADHD symptoms are usually more frequent in males than in females, which was also true in our sample (independent sample t-tests revealed a significant difference with $p = 0.006$). The effects of *SNAP25* might therefore be more apparent in males as a result of higher variance (and more extreme cases) compared to females.

5.1.2 Effects during development

The behavioural effects of the rs363039 polymorphism remained significant at both follow-up time points (figure 9). This genotype effect on behaviour shows an interaction with time of assessments but not with age, suggesting the effects we see on WM capacity are stable across childhood and adolescence but might be sensitive to test-retest effects.

There are two different isoforms of the SNAP-25 protein, SNAP-25a and SNAP-25b which show different expression throughout development. The SNAP-25b form is considered crucial for healthy development as mouse mutants that do not express this form show impairments in neuronal development and short term-plasticity as well as impaired cognitive functions (Bark et al. 1995). We saw that the genotype interacted with age for PCC structure, suggesting that it affects the development of this area. No age related effects were found for the behavioural data. We also found that grey matter density significantly correlated with WM performance in the youngest age groups only. It therefore seems plausible that *SNAP25* genotype has an effect on brain development in younger years, but that this effect has a long lasting, stable impact on cognitive functions.

5.1.3 Wider associations

The SNAP25 protein is of crucial importance for neural functioning throughout the brain. This implies that it is highly unlikely that effects of this gene would be limited to a specific cognitive function like WM. Indeed our results show that, in addition to WM, it is linked to a number of other cognitive tasks such as reasoning and reading ability. Furthermore, clinically, *SNAP25* is not only linked to ADHD but also to Schizophrenia and bipolar disorder (Carroll, Kendall, O'Donovan, Owen, & Williams, 2009; Corradini, Verderio, Sala, Wilson, & Matteoli, 2009; Etain et al., 2010); disorders that are also linked to altered activity in the DMN (Meda et al., 2012).

5.1.4 Conclusion and further directions

In conclusion, Study I and the recent preliminary analyses suggest a role for *SNAP25* in development of the brain, cognitive functions and symptoms of ADHD. The association found with deactivations in PCC points to an involvement of the DMN in these functions, something that has gained substantial attention in recent literature. Considering that these results are based on a typically developing sample, our results suggest that the effects of *SNAP25* are not only linked to clinically levels of ADHD but also affect functions within the normal distribution. This is in line with the ADHD often being considered to reflect an extreme end of a normal distribution (e.g. Sonuga-Barke & Halperin, 2010).

Results from Study I in combination with previous literature, suggest a spread effect of *SNAP25* both on various cognitive functions and on various neuropsychiatric disorders. In order to make sense of this information, we need to understand the effects of *SNAP25* function on the brain and how this can lead to diverse effects on the behavioural level. It has been suggested that a more specific impact early in development can have diverse consequences affecting functions that are apparently unrelated at a first glance, later in life (e.g. Karmiloff-Smith, 1998). It seems likely that *SNAP25* affects some fundamental brain function during development. Our results suggest that maturation and function of the PCC is one candidate for this influence. This fits well with the importance of PCC in the DMN and the emerging literature

pointing to the involvement of this network in many neuropsychiatric disorders (Corradini et al., 2009; Etain et al., 2010; Fair et al., 2010; Tomasi & Volkow, 2012). At the time of writing this thesis data were not yet been analysed to investigate if *SNAP25* genotype indeed influence the functional connectivity of this network. It will be important for future studies to investigate this in order to assess whether DMN function serves as a mediator for the associations observed for *SNAP25,* cognitive functions and different clinical symptoms. Ideally, activity and structure of the PCC should also be analysed with a longitudinal design, using the two follow-up measures that have been collected for the Brain Child sample, in order for us to be able to make more confident claims regarding the effects of *SNAP25* during development.

5.2 STUDY II AND III- TRAINING OF NVR AND WM IN HEALTHY PRE-SCHOOL CHILDREN

In Study II we show that reasoning ability can be trained through implicit cognitive training such as has previously been shown for WM in typically developing young children. This training was shown to lead to improvements on a latent variable measuring underlying *Gf*. Furthermore, training on NVR tasks resulted in transfer between constructs with improvements observed on a visuo-spatial WM task (Odd One Out).

Since the completion of Study II, similar results have been shown by Mackey and colleagues (Mackey, Hill, Stone, & Bunge, 2011). They compared training on commercially available computer games either emphasising reasoning or speed components in children aged 7 to 9 years. The children training on the reasoning demanding games improved on a reasoning task as well as a visuo-spatial WM task. However, there were no far transfer effects observed between the two components being trained.

In addition, Study II replicates previous studies by showing improvements on WM after WM training in typically developing children. However WM training did not result in significant transfer effects to measures of reasoning ability that has previously been reported (Jaeggi et al., 2008; Klingberg et al., 2005).

Study III shows that implementation of this training is also feasible for children with intellectual disability. However, although a large proportion managed to carry out the training intervention successfully, for some individuals this training did not lead to the benefits hypothesised, both considering the training progress and transfer to non-trained tasks. Thus it highlights the need to look at inter-individual differences that are discussed in more detail below.

5.2.1 Transfer effects after training in young children

We investigated if there is additional benefit gained from training on a combination of WM and NVR tasks. This was only found to be the case for the tasks similar to those

trained on. For most transfer tasks there was instead a dosage response in which more time spent training within a construct lead to greater transfer effects within that construct.

Jolles and Crone (Jolles & Crone, 2012) have recently pointed out that one reason for limited effects of training in young children might be the immaturity of brain functions or structures. For example during development there is a change in myelination and synaptic connectivity which are believed to influence the cognitive capacity. If, in a certain area, these have not reached a critical level of maturity (either due to young age or due to a clinical disorder altering or delaying development) it is possible that training might not have as large influence on functions relying on that area. We do not currently have knowledge regarding the neurological effects of training in this young age group. A mere speculation however, could be that if susceptibility for training influence increases with maturity, then one would assume that training in younger children affects parietal areas to a larger extent than prefrontal areas due to the earlier timing of maturation of parietal brain regions, discussed in the introduction. If hypothesised transfer between constructs (for example, between WM and reasoning ability) depends on common improvements in top-down control within the PFC, then such effects might not occur due to relative immaturity of the PFC. This could also be the result of lower levels of connectivity in the developing brain leading to PFC activity having less of an impact on other brain regions.

Training of WM has been shown to influence functional connectivity in adults whereas no such effects were seen for 12-year-old children (Jolles, van Buchem, Crone, & Rombouts, 2011). However the same group did show that WM training resulted in increased fronto-parietal activity resulting in activation patterns similar to those observed in adults (Jolles, van Buchem, Rombouts, & Crone, 2012), which, they argue, disputes the suggestion that some brain areas are not engaged by training due to their immaturity. It is currently unclear if similar patterns of effects would be found for children as young as 4 years and it is for future studies to explore this further.

Nonetheless, training at an early age can have great practical advantages. If one is able to identify children at risk for unfavourable cognitive development (for example children at risk of developing attention deficits), early intervention might have additional benefits from the direct effects, in that it might alter the developmental trajectory and thereby avoiding or decreasing unfavourable development and associated symptoms (Sonuga-Barke & Halperin, 2010). This approach ultimately avoids or decreases unfavourable development and associated symptoms. Our data then suggests that young children can train and can improve on both *Gf* and WM, but as the level of transfer between constructs were limited, it suggests that children should train on tasks directly within the constructs where improvements are desirable.

5.2.2 Inter-individual differences in training

Not only age is important for the level of plasticity, but previous experiences, genetic factors and clinical status can also be of importance. Study III highlights this by moving the focus away from traditional group analyses where an intervention group is compared with a control group, to a focus on an individual level. This study is the first to investigate cognitive training of this sort in a sample of children with intellectual disability. This is a very heterogeneous group both regarding severity of impairments and their aetiology, and thus the factors that might influence training achievement are also likely to vary considerable. Indeed we did observe great variance in the training progress, with some individuals improving steadily throughout the training period while other individuals reached just above the levels we used for the non-adaptive control group (the first three levels for NVR tasks). For the latter individuals, it would be incorrect to claim that the training had been successful, at least within our strict standards requiring significantly greater improvements compared to the non-adaptive control group.

We initially assessed the effects on transfer in children with intellectual disability based on a group level and found that training group predicted improvements on a number of transfer tests, although these were mostly weak trend effects. Then considering that a proportion of individuals in the adaptive training group remained on levels close to that of the non-adaptive training group, it seems likely that the transfer effects observed were driven by the individuals who increased more during training. This is taking into consideration that our intervention used a double-blinded design so that children, parents and the psychologists assessing the children were unaware of group belonging and that it is therefore unlikely that effects reflect an expectancy biases. The influence of training progress was confirmed in our additional analyses in which we looked at an individual's training progress as a continuous variable instead of the group variable. This showed that children who had increased more during training also showed greater transfer effects. These findings draw attention to the importance of looking at inter-individual differences in performance within the training group.

In a clinical group where great variance is expected it might be of particular importance to look at inter-individual baseline differences in an attempt to understand what factors can predict if a certain training will be successful or not. We took one step in this direction by performing analyses looking at baseline predictors of training progress. Our analyses revealed that baseline level of cognitive performance, gender and co-morbidity with additional neurological disorders all affected training in our sample. It would be desirable for future training studies to investigate this further, performing a more detailed baseline characterisation.

5.2.3 Conclusion and future directions

The results from studies II and III show that it is feasible for young children to train on NVR and WM tasks and that this can lead to substantial improvements in related cognitive measures. These findings also help us in the understanding of mechanisms

underlying improvements resulting from training. Results from Study III in particular, point to the importance of looking at inter-individual differences when evaluating the effects of a training intervention. However, more research is still needed for a more detailed understanding of what predicts a successful training. Hopefully in the future such information can aid us in designing new training paradigms that are adapted to an individual's needs. For example, some individuals might benefit from longer training periods, slower adaptation in difficulty level or more focused training (training only one cognitive construct at the time).

5.3 STUDY IV – THE EFFECT OF DAT1 ON TRAINING INDUCED PLASTICITY

In Study IV we provide additional evidence for inter-individual differences that predict the effects of training. We found that polymorphisms within the gene coding for dopamine transporter (*DAT1*) predicted transfer effects resulting from the training in Study II. The dopamine transporter removes dopamine from the synaptic cleft and therefore influence available dopamine concentrations. Variants within *DAT1* have been linked to available dopamine levels in areas of the basal ganglia (Heinz et al., 2000) which makes our findings relevant considering that striatal activity has been show to predict level of transfer (Dahlin et al., 2008), and basal ganglia activity has been related to unnecessary storage of distracting stimuli (McNab & Klingberg, 2008). We did not find effects of any of the SNPs on baseline level of capacity and therefore our results suggest that effects were related to the amount of plasticity as induced by the cognitive training. This suggests that *DAT1* might influence our cognitive abilities by mediating the effects of environmental influences. *DAT1* has previously been associated with ADHD, and in particular the T-allele of the rs27072 that we found to be associated with greater improvements following training has previously been suggested to have a protective effect for ADHD (Brookes et al., 2006; Feng et al., 2005).

5.3.1 Conclusion and future directions

Findings in Study IV show that variation in the *DAT1* gene influence the impact cognitive training has in different individuals. Thus, it provides an additional factor that can explain some of the inter-individual differences highlighted in Study III. It further provides additional support for the importance of dopamine, not only on WM function but also to the cognitive plasticity of WM and NVR functions.

Since genetic effects tend to be of a small magnitude, large sample sizes are required for sufficient power to detect these effects. In this light, Study IV is limited by its small sample. Therefore future studies including more participants are desirable for replication of these results and to further investigate the importance of other genetic variants on cognitive training.

5.4 GENERAL DISCUSSION - NATURE AND NURTURE

The long going debate on whether it is primarily nature (e.g. genetic factors) or nurture (environmental factors) that influence our cognitive abilities is, with the current knowledge, becoming irrelevant. There is, as has been described above, strong evidence for nature, in that the genetic setup that we are born with, has a large impact on our cognitive capacities including WM (Friedman et al., 2008). Furthermore, a recent study looking at performance on an intelligence tests suggest that the genetic variance accounting for performance at 11 years of age still explained a large portion of the performance on the same intelligent test some 70-80 years later in life (Deary, 2012). We show in Study I an example of how one specific genotype can affect brain structure and activity as well as cognitive performance.

On the other hand, the importance of nurture, in the form of environmental influences is undeniable. Training studies as discussed in studies II, III and IV can be viewed as a controlled, positive manipulation of the environment. This has been shown to have significant influence not only on behavioural measures but also on measures of brain activity, structure and neurochemistry. It seems clear that the experiences, challenges and encouragements that we meet in life all have the potential to impact on our abilities by changing underlying brain function.

It has recently been found that humans have a 12 fold increased expression of genes associated with development and plasticity as compared with our closest relative, the chimpanzee (Liu et al., 2012). This increased expression, observed in the PFC was also observed to occur during a longer period of childhood in humans. This suggests that one thing contributing to the development of our extraordinary cognitive abilities is our plastic brains, that is our ability to adapt to the environment we are in. If this is so, variance within these genes are also likely to contribute to the degree to which we are influenced by the environment today. This influence can be for better-or-worse, in that an increased level of plasticity can make an individual more predisposed to benefit from a beneficial environment but can also make an individual more vulnerable to negative environmental factors. This has been argued by Belsky and others in several studies and there is some specific evidence suggesting that genes involved in the dopaminergic pathway interacts with environmental factors to influence cognitive performance in this pattern (Belsky & Beaver, 2011; Belsky et al., 2009).

With the strong evidence for both genetic and environmental influences it is therefore becoming apparent that, to fully understand cognitive functions, one cannot ignore one or the other. Rather the genes we are born with and the environment we are placed in are likely to interact with each other in forming our brains and our cognitive abilities and as a result our behaviour.

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