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TRACKING AND PREDICTING COGNITIVE DEVELOPMENT USING MAGNETIC RESONANCE IMAGING

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Front cover:

An illustration of the future utility of MRI for the benefit of children born preterm. Sixteenth century illustrations of breech presentation and twinning, both common ways for preterm children to start their life.

Illustrations from “De Partu Hominis”, published 1532 by Eucharius Rösslin the Younger.

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I am putting myself to the fullest possible use, which is all I think that any conscious entity can ever hope to do.

— HAL 9000

Abstract

Neuroimaging of the developing brain has helped describing and quantifying many of the biological processes underlying cognitive development. The protracted development of higher order cognitive functions has allowed detailed description of their neural correlates. While primary sensory and motor functions have been found to be relatively localized, higher order cognitive functions including Working Memory (WM) have been found to be distributed over many brain regions. A growing amount of literature is describing a complex interaction of anatomically separate nodes making up networks sub-serving WM. The development of these networks is dependent on both predetermined maturation and environmental stimulation. The current thesis aims to expand the current knowledge by exploring if WM development can be predicted by using Magnetic Resonance Imaging (MRI) data explaining future development rather than correlating to current capacity. We further apply this principle on a sample of premature born children to predict future cognitive outcome using MRI at birth. Finally we address the question if individual variability in developmental timing affects cognitive abilities in childhood and adolescence.

Study I: In this study we show that WM development to some degree can be predicted using structural and functional MRI. The prediction was based on a multivariate model of MRI data and could significantly predict WM two years after the scans. This significance was retained after controlling for three concurrent WM tests. Analysis to localize the predictive effect of MRI suggests basal ganglia and thalamic structures as important for future development while classical cortical WM areas correlate to concurrent WM capacity.

Study II: We apply a similar analysis strategy as in Study I on a longitudinal sample of preterm born children. T2 and Diffusion Tensor Imaging (DTI) sequences were collected in

the perinatal period and used to predict WM and Numerical Ability (NA) at five and seven years of age. We show that multivariate models can predict NA and WM capacity at five years of age. This was the strongest predictor when compared with previously known important clinical features. T2 based volumetric analysis points towards reductions in insula and basal ganglia volume in the perinatal period among children with low cognitive function at five years of age.

Study III: The study explores weather the individual time course of development affects WM abilities when children start school. We trained a multivariate model of brain development using DTI from a sample of normally developing children. We then apply the model on a sample of seven year old children to show that brain maturation correlates strongly with WM abilities while age does not.

In summary the articles add to the developmental neuroscience literature by showing the ability of MRI to predict cognitive development. Prediction of development is an area discussed as a promising target for clinical implementation of cognitive neuroimaging. We show the feasibility and clinically relevant effects of prediction in a clinical sample. Finally the measuring of variability in developmental timing in Study III highlight the view of WM development as result of multiple processes.

List of publications

I. **Ullman H.**, Almeida R., Klingberg T. (2014). "Structural maturation and brain activity predict future working memory capacity during childhood development." In: *J. Neurosci.* 34.5, pp. 1592–8.

II. **Ullman H.***, Spencer-Smith M.*, Thompson D., Doyle L., Inder T., Anderson P., Klingberg T. (2015). "Neonatal MRI is associated with future cognition and academic achievement in preterm children." In: *Brain* 138.Pt 11, pp. 3251–62.

*These authors contributed equally to this work.

III. **Ullman H.**, Klingberg T. "Timing of white matter development determines cognitive abilities at school entry but not in late adolescence". *under review.*

Contents

List of abbreviations

MRI	Magnetic esonance imaging
fMRI	Functional magnetic resonance imaging
BOLD	Blood oxygen level dependent
WM	Working memory
ADHD	Attention deficit hyperactivity disorder
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
SVM	Support vector machines
SD	Standard deviation
NA	Numerical ability
GLM	General linear model
MNI	Montreal neurological institute
VBM	Voxel based morphometry
DBM	Deformation based morphometry
VSWM	Visuo-spatial working memory

Chapter 1

Introduction

1.1 Brain development

The human brain follows a protracted course of development compared to most mammals (Workman et al., 2013; Giedd et al., 1999; Pfefferbaum et al., 1994; Miller et al., 2012). Many different biological processes characterize this development. Different processes occur during different stages of development. Some processes such as neuronal migration are mostly complete at birth (Sidman et al., 1973; Rice et al., 2000) while others, such as myelination continue into the third decade of life (Benes et al., 1994; Paus et al., 2001). The delayed development of the brain enables environmental stimulation that is the basis of large environmental influence on brain development. The delayed development also allow us to study the maturation with neuroimaging. During the past decades many of the signatures of both normal and abnormal brain development and their cognitive reflections have been characterized using neuroimaging.

One of the great promises of advanced cognitive neuroimaging is to go beyond correlations of variability in brain and cognitive development and instead find abnormalities in brain development before they manifest in cognitive abnormalities (Gabrieli et al., 2015; Bray et al., 2009). The fulfillment of this promise would have a large impact on clinical medicine as it would open up a window for intervening if suboptimal development is predicted.

While the biological processes of gray and white matter development may be separated to a varying degree in space and time their interplay and dependency are evident from clinical (Inder et al., 1999; De Stefano et al., 2003) and pre-clinical studies(Fields, 2015; Demerens et al., 1996; Ishibashi et al., 2006). The failure of cortical development will lead to affected white matter development and vice versa(Bray et al., 2015). Despite this interdependence the processes of white and gray matter development must be considered partly separate as their development is driven by separate genes (Gleeson et al., 2000; Snipes et al., 1993).

1.1.1 Gray Matter Development

The cortex is formed as a result of neuronal migration that occurs to the largest part in utero (Bystron et al., 2008). Since little neuronal migration occurs after birth the experience dependence of this process it rather limited. The postnatal development of the cortex is characterized by the following three processes: 1) Synaptogenesis – The formation of synapses occurs predominantly during the early years of development but continues to a lesser degree throughout the lifespan (Huttenlocher et al., 1997). Formation of new synapses has been proposed as the major underlying mechanism of experience dependent behavioral plasticity in the adult (Zuo et al., 2005; Moser, 1999). Both outgrowth of axons, dendrites and strengthening of existing synapses may contribute to this process, outgrowth of dendrites in response to environmental stimuli has most consistently been shown in the literature (Holtmaat et al., 2009). 2) Apoptosis – Programmed cell death occurs pre- and post-natally. The largest rate of apopthosis occurs during the early years of development (Rosa et al., 2000; Rakic et al., 2000). The apoptosis is regulated by neurotropins secreted by neurons and glia cells (Huang et al., 2001). Less connected neurons have a larger chance of undergoing apoptosis (Okado et al., 1984; Ikonomidou et al., 1999; Heck et al., 2008). 3) Synaptic pruning – The removal of existing synapses continue up into adulthood (Petanjek et al., 2011) and is experience dependent (Mataga et al., 2004).

On a macroscopic level the thickness of the cortex changes during childhood and adolescence. The neocortex follows an elliptic trajectory with an initial increase in thickness during early childhood followed by a slow decrease in thickness. The time course of the development differs between regions with primary sensory cortical areas reaching their maxi-

mal thickness early and parietal association and prefrontal cortices reaching their maximum thickness later (Giedd et al., 1999; Gogtay et al., 2004; Sowell et al., 2004).

1.1.2 White matter development

The white matter fills the space between the ventricular zone and the cortex. While initially occupying a relatively small volume during the morphological development there is a rapid increase in volume during late gestation (Dubois et al., 2014) followed by maturation during the first two years of life (Mukherjee et al., 2002; Dean et al., 2015). This increase in volume is to some degree an effect of the axonogenesis of developing neurons in the gray matter but to the largest degree this is an effect of the proliferation and maturation of glia cells(Thomas et al., 2000; Baumann et al., 2001).

Myelination is one of the most striking processes in the development of the white matter. This is the process of increased content of myelin produced and stored in oligodendroglial cells surrounding axons(Hardy et al., 1996; Thomas et al., 2000). Proliferation of the oligodendroglial cells occurs predominantly in utero and is followed by myelination during late gestation and after birth (Back et al., 2001). While the majority of myelination is complete by two years of age (Barkovich et al., 1988; Graaf-Peters et al., 2006), the process continues, albeit at a slower rate into the third decade of life (Barnea-Goraly et al., 2005; Giorgio et al., 2010; Klingberg et al., 1999). There is also a gradient in the timing of white matter with primary sensory areas myelinating early and associative areas myelinating later (Barkovich et al., 1988, Brody et al., 1987).

1.1.3 Functional development

In parallel with the previously described anatomical development of the brain there is also a progressive change in the activity in the anatomical networks. The term functional development refers to this change in brain function as opposed to the anatomical development of the brain. More specifically, the modality most extensively used for studying the functional development of the human brain is fMRI. The method measures neural activity indirectly through the susceptibility differences in oxygenated and deoxygenated hemoglobin, a proxy measure of regional neuronal activity (Ogawa et al., 1990; Kwong et al., 1992).

The analysis of fMRI in developmental samples can generally be divided into two groups, activity dependent and resting state fMRI. Activity dependent fMRI measures the change in BOLD signal in response to a change of mental state, often induced by an external stimulus. Resting state fMRI instead looks at the spontaneous fluctuations in BOLD signal occurring in rest.

Activity dependent fMRI

Activity dependent fMRI studies on developmental samples have shown that there is a correlation between activity dependent BOLD signal for motor (Schapiro et al., 2004), as well as higher order cognitive tasks such as Working Memory (WM) (Klingberg et al., 2002; Kwon et al., 2002 ;Crone et al., 2006; Scherf et al., 2006; Jolles et al., 2011) with age. An increase in BOLD signal magnitude thus accompanies the rise in both motor and cognitive function during development.

Resting state fMRI

The biological importance of the spontaneous BOLD fluctuations was first demonstrated in primary motor regions (Biswal et al., 1995). The cortical areas show distinct patterns of resting state correlation that appears to follow functional dependence and anatomical connectivity rather than anatomical proximity and has been named resting state networks (De Luca et al., 2006; Damoiseaux et al., 2006). These resting state networks have been shown to emerge and differentiate during development (Dosenbach et al., 2010). While resting state fMRI is not used in the current thesis the field is relevant as much of the methodological development that this thesis builds upon gained usage through resting state fMRI (Heuvel et al., 2010). The technique has also been proposed as better suited for clinical use than activity dependent fMRI as no active participation is required (Fox et al., 2010).

1.2 Cognitive Development

There is a dramatic development of a broad range of cognitive functions from the first years of life with a slower increase that continues through adolescence (Roalf et al., 2014; Gathercole et al., 2004; De Luca et al., 2003). As the performance on different functions show

greater improvements in certain age ranges it is important to measure and study these separately. For example non-declarative memory is thought to develop earlier than declarative memory as it is not dependent on the immature hippocampus (Perez et al., 1998) and WM continues to develop after both of these systems (Gathercole et al., 2004), presumably due to the protracted development of pre-frontal cortex (Shaw et al., 2008).

Due to the large degree of development that takes place after birth cognitive function develops under constant environmental influence. The late development of higher order cognitive function leaves even more time for environmental influences. As most biological development the cognitive phenotype is a result of genes and environment. Regarding functional brain development, more specific descriptions of how genes and environment interact have been described (Johnson, 2001). A few general mechanisms for the developmental processes can be separated. The first is maturation, which describes the purely genetically predetermined part of development (Davies et al., 2011). An example of this is the morphonegesis of the brain that is determined by chemical signaling independent of the environment (Rubenstein et al., 1999). The second principle is skill learning, which points to the environmental stimuli as a cause of promoting an increase or change in function. On a neuronal level this can be represented in a change or fine tuning of an existing neuronal network. While this process is most classically associated with the acquisition of procedural or declarative memory, it may also apply to the development of higher order cognitive functions (Klingberg, 2014). The last is the concept of interactive specialization. This refers to the successive specialization of brain areas in response to environmental stimuli. While sharing the emphasis of the environment with skill learning, the concept refers to the development of compartmentalized brain functions in successively more specialized areas in response to environmental stimuli (Johnson, 2000). Behaviorally however the latter two processes may be indistinguishable. An example of interactive specialization is the development of a specific cortical area that is activated by reading words (Schlaggar et al., 2007). While functional specialization is well established and serve as rational for parcellation analysis of neuroimaging data (Cohen et al., 2008), it is important to note that no function is strictly located in a specific area in the sense that the area is necessary and sufficient for function.

While cognitive development parallels the anatomical and physiological development of the brain it is important to note that a discrepancy in biological measures and psychological

measures of development exists. Correlations between cognitive functions such as WM to biological data from Neuroimaging studies data are expected to be lower than the internal validity of any test, often described by test – retest correlation. Higher correlations than this may be inflated due to the statistic analysis used (Vul et al., 2009). This unexplained variance may be due to measurement noise in both the psychological and neuroimaging measures. Psychological measures must always be the gold standard to which biological correlates are judged . This may be a problem for clinical applications of neuroimaging in psychiatry. As long as disorders are defined by behavior, concurrent biological measures may only serve as noisy and redundant tests (Kapur et al., 2012; Gabrieli et al., 2015).

To find clinical use of cognitive neuroimaging it is important to concentrate on psychological measures that are both relevant for real world functioning and that have a measurable brain correlates. It is also of high importance to chose measures that have a high internal reliability, i.e it has a high test-retest correlation. The internal validity of many standardized cognitive tests fall within the range of Pearson correlation 0.7-0.8 for clinical groups (Watkins et al., 2013; Green Bartoi et al., 2015), which is higher than most fMRI evaluations (Plichta et al., 2012; Brandt et al., 2013). This gap may though be decreased by improvement of the fMRI protocols used today (Andellini et al., 2015).

1.3 Working memory

1.3.1 The relevance of Working Memory

One of the cognitive constructs that fulfill all the criteria listed above is WM. WM is defined as the ability to keep information in the minds eye for processing (Baddeley, 1992). In this thesis WM was chosen as it has been extensively studied in terms of its developmental pattern (Gathercole et al., 2004; Luciana et al., 1998; Luciana et al., 2005), relevance for academic and work performance (Bull et al., 2008; Bayliss et al., 2005; Lee et al., 2013). Robust neuroimaging correlations in multiple modalities have also consistently been shown (Bunge et al., 2007; Nee et al., 2013), ensuring that technical development has reached the point where it can be used for modeling WM development.

1.3.2 Neuroimaging and Working Memory

Standard measurement scales of WM can give reliable measures from an age of around 6 years of age (Wechsler, 2014). At ages lower than this the measurements may be unreliable, warranting different measurement scales (Nutley et al., 2010). From the age of reliable measures of WM, WM has consistently been shown to be tied to structures in the parietal lobe and pre-frontal cortex (Klingberg, 2006). Univariate analysis of fMRI has consistently shown a correlation between the WM task induced BOLD signal in superior and inferior pre-frontal cortex as well as in the superior parietal lobule and WM capacity (Klingberg et al., 2002; Kwon et al., 2002; Crone et al., 2006; Scherf et al., 2006; Geier et al., 2009; Jolles et al., 2011). Basal ganglia has also been shown to be activated during WM tasks (Klingberg et al., 2002; Ziermans et al., 2012) but the activation has not been shown to correlate to WM load. Structural development of these cortical areas has been correlated with WM capacity (Tamnes et al., 2013), but the finding has been less replicated than the fMRI findings. The development of WM related cortical areas does however correlate strongly with age (Shaw et al., 2006), and delays in development are associated with ADHD (Shaw et al., 2007), a disorder characterized by WM deficits (Martinussen et al., 2005). The individual trajectory of BOLD and cortical volume do however not seem to correlate (Squeglia et al., 2013), stressing that multiple neuroimaging modalities are needed for accurately track brain development. White matter development as measured with DTI is also strongly correlated with development. FA, a measure of white matter microstructure, shows a marked increase during development. The biological substrate for this change is thought to be driven mainly by myelination (Beaulieu, 2002; Concha et al., 2010) but other processes such as axonal density may also affect the measure and may be distinguished using data modeling (Sepehrband et al., 2015). There is a relationship between FA in the white matter tracts that connect the parietal and prefrontal WM areas (Olesen et al., 2003).

1.4 Numerical ability

1.4.1 The relevance of Numerical Ability

Numerical ability is investigated together with WM in the thesis. It is defined as the ability to recognize numbers, their value and numerical manipulations. In the thesis it was measured using tests asking children to identify, count and solving simple mathematical problems. The development of numerical ability starts during the first years of life and continues through adolescence (Geary, 2000). Just as WM it has been shown to specifically predict children's academic achievements (Cowan et al., 2011). There is a strong correlation between WM and numerical ability (Raghubar et al., 2010), illustrating that they likely share much of their neural substrate. There are however specific features of numerical ability that may be separate from WM (De Smedt et al., 2013). Preterm born children also show lower numerical ability which highlights the clinical relevance of the measure (Simms et al., 2013).

1.4.2 Neuroimaging of Numerical ability

Studies using fMRI to localize cortical areas related to numerical ability have shown activations in parietal and prefrontal regions during numerical tasks (Dehaene et al., 2004). During development there appears to be a shift where children engage pre-frontal areas and adults engage parietal areas (Houdé et al., 2010). The intra parietal sulcus, is the cortical area that has been most specifically described as related to numerical ability (Dehaene et al., 2003). There is however an overlap with the cortical areas activated by WM tasks (Zago et al., 2008).

1.5 Machine Learning and MRI

During the first couple of decades after the advent of cognitive neuroimaging researchers primarily looked at univariate correlation between cognitive states or traits and brain activity. Collectively these kind of analyses are names brain mapping as they aim to entangle the functional architecture of the healthy brain and what functional areas that show alterations in illness (Lancaster et al., 2000). Distinct compartmentalization of functions into anatomically distinct areas is only partial, especially for higher order cognitive functions where multiple

regions are activated and overlap in the activation for many distinct cognitive tasks is high (Culham et al., 2001; Yeo et al., 2011). The distribution of higher order cognitive functions is also evident in lesion studies where a wide variety of lesions can produce the same WM deficits (Müller et al., 2006). Functional MRI studies have revealed that looking at local patterns of BOLD signal allows far more detailed predictions of what visual information that is processed than using classical univariate analysis as the same cortical regions are activated by many similar stimuli (Haxby et al., 2001). The evidence thus point to a representation of information in the cortex that is to some degree compartmentalized but also distributed on a local level withing regions activated during a specific task. Thus, in order to model and measure cognitive functions as accurately as possible with neuroimaging data, one should employ statistical methods looking at multivariate effects, or patterns (Varoquaux et al., 2014). By looking at multivariate effects, one can theoretically find relationships between brain measures and cognitive states or traits that is not possible using univariate analysis. Consider the simple illustration of this possibility in figure 1.

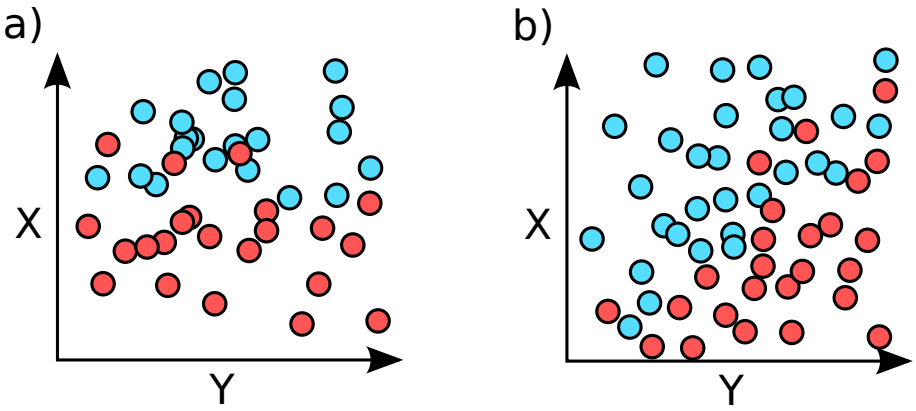

Figure 1: A simple illustration of a univariate and multivariate effect in two dimensions. X and Y are two features of the red and blue data points. In a) there is a univariate effect where the blue and red class can be almost completely separated along the X dimension. In figure b) neither X or Y can alone separate the classes well, but if analyzed together a good separation of the red and blue classes can be achieved.

Even in the lack of such multivariate effects including many voxels in a statistical analysis can give more robust measures just by integrating the information from multiple voxels of the

same underlying effect, thus reducing the amount of noise. Averaging signal over multiple neighboring brain regions is something that has been used in fMRI studies for many years in the form of gaussian smoothing of the MRI volumes (Friston et al., 1995a). However, this results in a loss of signal, especially in the localized patterns of BOLD signal that has been shown to carry important information (Kriegeskorte et al., 2006).

The evidence thus points to better understanding of the brain representation of cognitive states and traits by looking at multiple brain regions simultaneously. Combining neuroimaging modalities might also provide increased understanding(Sui et al., 2011; Zhu et al., 2014). It may be possible to find patterns when combining structural and functional neuroimaging that can predict function or traits which cannot be predicted when analyzing the modalities separately. Methodological studies have shown that multi-modal combination may not always prove beneficial (Pettersson-Yeo et al., 2014), this may however be dependent on the problem.

While integrating multiple measurements across the brain and between modalities may allow higher performance in predicting cognitive states or traits, one concern with the approach is that the complexity of the models increase. Model complexity is problematic for two primary reasons. The first reason is that a more complex model may be more susceptible of over-fitting. A practical example of this is that a complex polynomial model is more susceptible to measurement error in the data which can lead to over-fitting and non-generalizable models. These models may accurately model the dataset when the model is fitted but fail to replicate the findings on a new dataset. Over-fitting can be dealt with using different statistical approaches as discussed below.

The second problem with multivariate models is that of human interpretation. Univariate analysis of neuroimaging data is typically done using general linear models. Linear, univariate models are easily interpreted and thus easily accepted by medical scientists and clinicians. Multivariate models capture not only the univariate effects but also the relationships between the predictors. When the number of predictors used in the model becomes high the model is hard to interpret intuitively. Furthermore, multivariate models often use non linear models which makes interpretation even harder. This problem has limited the acceptance of multivarate models for clinical applications of advanced neuroimaging as they may be perceived as a black box (Foster et al., 2014).

The studies included in this thesis use statistical methods that are often referred to as machine learning methods. The term machine learning stems from computer science and has been defined as making "computers the ability to learn without being explicitly programmed" by Arthur Samuel. The use of the term in neuroscience and most biomedical fields instead point to constructing multivariate statistic models using datasets that contains a large number of variables. Machine learning models often aim to find complex relationships in the data that might be difficult to find and describe using univariate methods.

One central concept in machine learning is the division between supervised and unsupervised models. The studies in this thesis use both groups of models. Supervised machine learning is used when an outcome class or continuous variable is known. The models aims to find relationships between the data and this outcome variable. An example is the commonly used Ordinary Least Square regression. The other group of analyses is the unsupervised group. These analyses are used when no prior class or outcome variable is known. Unsupervised machine learning instead focus on finding intrinsic patterns in the unlabeled data. A common unsupervised machine learning method is K- means clustering.

1.5.1 Support Vector Machines

Among the supervised machine learning models Support Vector Machines (SVM) have gained attention in cognitive neuroimaging due to it's good performance in noisy data. It has been used to decode mental states from fMRI (Haxby et al., 2001). SVM was originally a classification algorithm but has been extended to regression problems(Cortes et al., 1995; Schölkopf et al., 1998). Its robustness to noisy data comes from only using a subset of data points for fitting the function that forms the classification boundary or regression line. This subset of data points are named support vectors since they support the model. This property makes the model resistant to noisy data points as extreme outliers may be excluded from affecting the model. Another central feature of the SVM is the use of kernel functions to transform the input data into second data-space where the model fitting is done. There are multiple parameters that have to be set when fitting the SVM model. These can be selected to suit the data in the model. The type of kernel function also has to be selected. The kernel complexity rages from linear kernels to polynomial functions and even more complex radial basis functions.

1.5.2 Feature reduction

One of the problems with applying SVM and similar multivariate models on neuroimaging data is the high number of voxels and a relative low number of samples. When this is the case models run a high risk of over-fitting the data, that is fitting noise in the data resulting in a model that will not generalize to new datasets. This can be dealt with, as mentioned above by reducing the complexity of the model, for example, by using linear kernels. Another strategy is to use some algorithm to select the most important predictors from your data. This is termed feature reduction (Mwangi et al., 2014). Many feature reduction algorithms have been used in the literature (Pereira et al., 2009). There are also approaches that tries to use the functional cortical areas as a base for dividing MRI signal into fewer features (Cohen et al., 2008).

1.5.3 Cross validation

When evaluating multivariate models such as SVM, one can in most cases not evaluate the performance of the model based on the goodness of fit. As a sufficiently flexible model will always be able to explain a large amount of variance in the dataset. In order to know if this explained variance is a true relationship or noise a second test on an independent dataset is needed. In cases where a second independent dataset is not available a cross validation approach can be used. In cross validation the dataset is repeatedly split into testing and training datasets and the model predictive ability for each sample is evaluated based on a model that is independent on it. This approach has been shown to be a very good approximation of how well a model generalize to an independent dataset in neuroimaging (Pereira et al., 2009).

1.6 Machine learning in clinical neuroimaging

Despite the interest and number of high quality publications using machine learning in pre-clinical neuroimaging, the clinical adoption of the results is low. The technical complexity of multivariate models make them hard to interpret. From the physician or clinical psychologists point of view complex models that are not understandable intuitively may not seem

trustworthy (Foster et al., 2014). One gap in methodology that needs to be filled in order to bring many of the neuroimaging studies using machine learning to the clinic is to present multivariate models so they intuitively can be understood.

There is also a difference in the types of data that are available for the neuroscientist and the clinician. Datasets used in research are very homogeneous as much effort is put on minimizing any possible differences between the subjects that may interfere with analyses. If the clinician wants to apply results based on these kind of datasets in practice, data collected in the same manner is needed. Neuroimaging data used in clinical evaluations are however in most cases less standardized which makes the multivariate models trained on homogeneous data unreliable. The nature of the variables of interest is also important to consider when comparing preclinical and clinical neuroimaging. Basic cognitive neuroimaging aims to broaden the knowledge in the field irrespectively of clinical usability of the results. As a consequence, many of the correlates between brain measures and cognition are either not clinically relevant or have an effect size that doesn't make them clinically significant. Despite these differences in the agenda between preclinical research and clinical practice, there are many possible applications of preclinical cognitive neuroimaing on clinical practice, one of which this thesis presents.

One of the possible application of cognitive neuroimaging in the clinic is that of cognitive predictions. While psychological assessment is the gold standard for cognitive assessment neuroimaging may provide a tool for prediction of future cognitive function. While psychological assessment is only able to capture the current cognitive state, neuroimaging may be able to measure developmental processes that will predict the future change in function (Gabrieli et al., 2015). In many patient groups this would provide information that would alter the clinical workup and possibly prevent undesired outcomes.

From a clinical perspective the patient groups for which multivaraite analysis of neuroimaging may be most suitable are those who have a pattern of pathology that is consistent across patients. Diseases characterized by focal brain lesions often show a large variation in the anatomical distribution. This makes automated analysis difficult as the model has to be able to find pathologic areas and take the distribution into account when making inference. On the contrary, two groups of diseases that are well suited for the application of machine learning models are neurodegenerative diseases and developmental disorders. These groups

have an associated neuroimaging pattern that shows a relatively similar distribution across patients. The distributed, and subtle pattern of changes also makes it harder to detect abnormalities by visual evaluation. An example is that visual evaluations of MRI from patients with ADHD are most often read as normal while widespread cortical and sub-cortical differences are frequently reported on group level (Shaw et al., 2007; Castellanos et al., 1994).

1.6.1 Preterm born children

Children born preterm is one group that would be hypothesized to benefit from introduction of the above mentioned techniques into the clinic. In this thesis the group serve as an example of successful application of methods developed in pre-clinical neuroimaging on clinical samples. From the literature premature birth is known to be a risk factor for reduced cognitive performance (Anderson et al., 2003; Johnson et al., 2009; Hutchinson et al., 2013) and neurodevelopmental diagnoses (Bhutta et al., 2002). Many clinical factors from the neonatal period (Woodward et al., 2006) and lesions visible on neonatal MRI (Murray et al., 2014) is known to be predictive of cognitive outcome. However, current clinical and neuroimaging predictors can only partly predict the cognitive outcome in the children. The brain changes resulting in later cognitive problems must be assumed to be already present at the end of the neonatal period. A gap in what clinical medicine is able to predict with current methods and what is theoretically possible therefore exists. There is also a clear benefit for the patients if cognitive development may be predicted at an early age. Predicted problems may be prevented or mitigated at an early age using cognitive interventions before they manifest in school problems.

Chapter 2

Aims and hypotheses

The general goal with the studies included in the thesis was to explore how cognitive development can be tracked and predicted using structural and functional MRI and multivariate methods. Initially, the analyses focused on exploring the methods in healthy children. These first results were then used in further investigations for clinical application as well as more in depth study of the trajectories of cognitive development in children and adolescents.

The studies were designed with both interest for basic neuroscience and clinical applicability in mind and with the goal of promoting clinical applications for advanced neuroimaging.

2.1 Study I

The first study in the thesis was designed to explore the feasibility of using MRI to predict cognitive development. A set of 62 healthy developing children from a sample recruited from the community and followed for two years was used. This sample was part of a larger sample of children that underwent psychological evaluation (Söderqvist et al., 2010). Using structural an functional MRI from the beginning of the study, statistical models were created with the aim of predicting the change in cognition at the follow up time point. The study draws from previous publications showing that the development of the brain can be tracked with both functional MRI (Dosenbach et al., 2010) and structural MRI (Franke et al., 2010). While these studies are cross sectional in design, we aimed to use a longitudinal design that would allow individual predictions. The main rational behind the study was twofold. The

first was to explore the possible practical use of MRI to supplement cognitive test by adding information not accessible to the cognitive evaluation. The second goal was to differentiate between the neural correlates of concurrent WM capacity and that of the future change in WM. This goal would be of high interest to basic neuroscience as one may separate networks important to develop cognitive function in contrast to those important to maintain it.

2.2 Study II

In study II we drew from the results in the first study and wanted to extend them to a clinical sample as well as replicate the fact that cognitive development could be predicted in developing children. The study aimed to predict cognitive development in extremely premature born children, a group that are well described to be at risk for reductions in WM and numerical ability that in turn affect academic ability. Using a longitudinal dataset of 224 children that had gone through MRI in the neonatal period and followed up with cognitive evaluations up until 7 years of age we aimed to see how cognitive predictions compared with those obtained from previously published clinical predictors of functional outcome (Woodward et al., 2006).

2.3 Study III

In the third study we aimed to explore how the patterns of brain development vary between different individuals and how this will affect the predictions that can be made. Given the variability in the time course of general development of the child we hypothesized the same to be true for cognitive development. The previous studies did not take the individual developmental course into account and may therefore not perform optimally as this variability will lead to error in the predictions. We predicted that variability due to individual developmental time courses would be prominent in younger ages but would diminish as children reach their developmental asymptote.

Chapter 3

Methods

3.1 Participants

In the studies a number of different samples of children were recruited. For the first study a sample of healthy children were recruited from the community by a questionnaire sent to families through the Swedish population registry (Söderqvist et al., 2010). The approach of this random selection minimized biases occurring by non equal distribution of socioeconomic status. This sample, hereby called the developmental sample, was a close to uniformly distributed sample of children in the ages between 6 and 20 years of age. The sample included 8 age groups whose age was separated by a two year interval. The sample included a larger group or 380 children that went through only psychological testing and a subsample of 90 that also went through MRI. In this thesis only a group belonging to the subsample that went through MRI was analyzed. Exclusion criteria for this sample was having a first language other than Swedish, sensory impairment or other neurological or psychiatric disorders. The exception was ADHD which was not an exclusion criteria. The sample was followed for 6 years with cognitive and MRI evaluations every two years. Three time points was thus available, allowing longitudinal analysis of cognitive and brain development.

For study II a longitudinal dataset of premature children was used. The sample consisted of children born at <30 weeks of gestational age and, or with birth weight of <1250 g at the Royal Childrens Hospital in Melbourne between July 2001 and December 2003. The sample included at total of 224 children. A control group of 46 term borne children from the same hospital was also used in the study. The children went through MRI scanning at

term equivalent age and were followed and evaluated by psychologists at 5 and 7 years of age. Children with congenital anomalies as well as lesions large enough to produce changes in anatomy were excluded. During the neonatal period, a large amount of clinical data was also collected (Woodward et al., 2006).

For study III a second sample of school children was recruited, hereby called the cognitive training sample. This sample consisted of 31 children at the age of starting Swedish primary school. Their mean age was 6.8 years with a SD of 0.3 years and thus had a very narrow age range in comparison with the developmental sample. Half of the sample was selected on the base of lower scores on a screening test in numerical ability and the other half was a random selection from a public school. The children were evaluated cognitively and went through an MRI examination before enrolling in a cognitive training program. After completing the program the children were again evaluated with cognitive tests as well as MRI. In this study only the pre-training measures were used.

All studies were approved by the respective ethical comities of the responsible institutions. The ethical committee of Karolinska Institutet approved the data collection and analysis of the developmental and cognitive training sample. The ethical committee of Melbourne University approved collecting the preterm born children sample and the data analysis. Informed consent was obtained from the parents of all children under 18 and from the children themselves if they were older than this.

3.2 Cognitive evaluation

Cognitive testing was performed in all samples included in the current study. In the developmental sample evaluation was carried out three times with two year intervals. In the premature sample cognitive evaluation was carried out at 5 and 7 years of age. While higher order cognitive functions may to some degree be measured prior to this age (Nutley et al., 2010) the measurements are less reliable. In the cognitive training sample children were evaluated with cognitive tests two times, one before and one after a five week program of training WM. Cognitive tests were either computerized or administered manually by a qualified instructor.

3.2.1 Working memory

WM was evaluated in all samples. The developmental sample was evaluated by three tests. One was the grid test from Automated Working Memory Asessment, a computerized visuo-spatial WM test (Alloway, 2007). The second was a backwards digit test in which the children are asked to remember a sequence of numbers and recall them in backwards order. The third test was a verbal 3 back test. The participants are asked to listen to a series of words and report whether or not each word is the same as the word read to them three words earlier.

In the preterm born sample WM was evaluated using the Backwards Digit Span Test from the Working Memory Test Battery for Children(Pickering et al., 2001). This test was similar to the previously described backwards digit test. The children were asked to listen to a string of digits and recall them in reverse order.

In the cognitive training sample the same working memory testing as for the developmental sample was carried out.

3.2.2 Numerical ability

Numerical Ability (NA) was only used for the preterm born sample and the cognitive training sample. In the preterm sample it was measured by two tests. At five years of age the children performed the Kaufman Survey of Early Academic and Language Skills test (Kaufman et al., 1993). From this test the Number Skills Scale was used. For this scale the children are asked to select or name numbers, count and solve simple numerical problems. At 7 years of age the children performed the Wide Range Achievement Test (Wilkinson et al., 2006). For this test the children are asked to count and identify numbers as well as solve simple oral and written math problems.

For the cognitive training sample NA was evaluated using three tests; the verbal arithmetic ability test from Wechsler Intelligence Scale for Children-IV, a computerized addition test and a computerized subtraction test.

3.3 MRI data

MRI scanning was carried out in all samples. MRI is a non-invasive technique based on Nuclear Magnetic Resonance. The adaption of this technique to obtain three dimensional images of the human body uses radio waves to alter the spin of electrons in a strong static magnetic field. The exited electrons will emit radio waves when the altered spin realigns to the magnetic field. This echo is dependent on tissue properties which is the basis for the reconstructed images. In addition to the strong static magnetic field weaker magnetic gradient fields are used for obtain spatial selectivity of the signal, allowing signal separation in three dimensions. In the absence of magnetic or paramagnetic material in the body, no adverse effects on the human body has been found despite four decades of clinical use (Schenck, 2000). The samples used in this thesis were evaluated with multiple MRI sequences listed below.

3.3.1 Anatomical imaging

Anatomical imaging was used in the developmental sample and the preterm born sample. T1 and T2 volumes are obtained by commonly used anatomical MRI sequences. The volumes indicate the T1 and T2 relaxation times of tissues which provides good contrast between many tissue properties of interest such as water and fat content. These volumes are used in the current thesis to conduct volumetric analysis of the brain.

In the developmental sample a T1 MPRAGE sequence with an isotropic 1 mm^3 resolution was obtained using a 1.5 T scanner. These volumes provide good contrast between white and gray matter and is thus suitable for volumetric analysis. For the preterm born sample T2 volumes was used for the volumetric analysis. In the neonatal, largely unmyelinated brain, the contrast is better between gray and white matter in T2 volumes making it more suitable for volumetric analyses in this age group. The images was acquired using a 1.5 T scanner and the voxel sizes were 0.43x0.43 mm^2 in plane and slices 1.7mm or 3mm thick.

3.3.2 Functional MRI

As previously discussed fMRI utilize local regulation of cerebral blood flow as a proxy measure of neuronal activity. In this thesis fMRI was used in study I for the developmental

sample. The MRI sequence consisted of an T2* Echo Planar Imaging sequence with TR = 3 seconds and voxel size of 3.44 x 3.44 x 4.5 mm. A task related WM sequence was used to measure the BOLD signal related to WM. The subjects were instructed to remember a sequence of dots on a 4x4 grid and subsequently answer questions about the location of the displayed dots. Trials where the subjects gave the correct answer were compared to a control condition in which dots were shown on set positions thus no load was put on WM. The General Linear Model was used to used. The explanatory variables were convolved with a canonical hemodynamic response function (Friston et al., 1995b). The analysis resulted in individual parametric maps of the beta parameter estimates from the General Linear Model(GLM). These maps were used in further analysis.

3.3.3 Diffusion Tensor Imaging

DTI was used in all samples. The technique uses dephasing and phasing of electrons in a strong static magnetic field to measure the degree of diffusion along a direction that can be decided by a magnetic gradient. By collecting 6 or more diffusion directions a 6 parameter tensor model can be fit to the data. This tensor model can be illustrated by an ellipsoid where 3 of the parameters describe the eigenvectors, that is the diffusion orientation in three dimensions, and 3 eigenvalues that determines the diffusion amount in three dimensions. The eigenvalues can be used to calculate a metric named Fractional Anisotropy (FA) that indicates the preference of diffusion along one dimension, that is the degree of elongation of the ellipsoid. This measure has been shown to be highly sensitive for development of the white matter and was therefore used (Barnea-Goraly et al., 2005; Giorgio et al., 2010).

In the developmental sample a 20 direction DTI sequence was collected using a 1.5 T MRI scanner. In the preterm born sample a line scan diffusion sequence with 6 gradient directions was used using a 1.5 T scanner. For the cognitive training sample 32 gradient directions obtained with a 3 T scanner was used. The tensor model was fit to the data after eddy current correction and FA volumes were calculated. These FA volumes were the base for subsequent analysis.

3.4 Software

A number of software was used for performing the analysis in the included studies. MRI data preprocessing and normalization relied on implementations included in FMRIB software library (Jenkinson et al., 2012) and the Advanced Normalization Tools (Avants et al., 2011). For statistical modeling the studies relied on the python programing language (www.python.org) as well as modules such as Scikit Learn (Abraham et al., 2014), Matplotlib (Hunter, 2007) and libsvm (Chang et al., 2011). For univariate exploratory analysis the Statistical Parametric Mapping implementation of GLM analysis was used (Friston et al., 1994).

3.5 Analysis

The analysis of the MRI data included imaging specific analysis and more general statistical analyses. The imaging specific analyses are mainly for preparing the data to make it available for use in more general statistical models. This includes mainly eliminating possible bias in the image, transforming the images into a common volumetric space and modality specific modeling to calculate parametric maps of interest. After these imaging specific analyses the statistics are generally the same as applying the statistical models for the analysis of other types of data. Here the imaging specific and the more general statistic analyses will be described separately.

3.5.1 MRI analysis

Normalization

In order to be able to apply quantitative analysis on MRI data it needs to be arranged into a common space. The most commonly used space is the Montreal Neurological Institute (MNI) space (Grabner et al., 2006). To transform the individual images to this space a template image is used as a target for an image transformation algorithm. In the studies presented here we used both linear affine algorithms and non-linear algorithms. Once the individual data is represented in the MNI space quantitative analyses were applied.

Voxel Based Morphometry

For measuring the variability in the size of anatomical structures in study I, Voxel Based Morphometry (VBM) was used. The technique measures the relative volumes of brain structures by segmenting anatomical MRI images into white and gray matter. The segmented images are normalized to a standard template using a non-linear algorithm and then multiplied with the Jacobian determinant for this transformation. Subsequently, these transformation modulated intensity images are then used for statistical analyses (Ashburner et al., 2000).

In study I VBM based on T1 weighed images was used as one of the modalities to predict cognitive development in the developmental sample.

Deformation Based Morphometry

Deformation Based Morphometryi(DBM) (Ashburner et al., 1998) is a technique related to VBM. The main difference lies in that no segmentation is done, and thus no tissue specificity is acquired. While the absence of tissue specificity limits the conclusions that can be drawn from the method it can be used when tissue segmentation of the images are not reliable.

In study II, DBM was used as the basis for analysis of local brain volume as the data did not allow accurate tissue segmentation.

Functional MRI

In Study I, WM task based fMRI was used as one of the predictors to predict cognitive development in the developing sample. The basic technique of fMRI was used as described above. The resulting parametric maps indicated the local BOLD increase, as described by the beta coefficient in the GLM. These individual maps were subsequently used for multivariate analysis.

Diffusion Tensor Imaging

DTI was used in all studies included in the thesis. A standard six parameter tensor model was fit to the diffusion sequences. The parametric FA volumes was obtained for each subject and this was subsequently used for multivariate analysis.

3.5.2 Data modeling

After the preprocessing steps described above the imaging data was modeled to predict the outcomes of interest of the study. The data modeling employs general statistical algorithms and is thus not specific for the analysis of MRI or neuroimaging data.

Feature reduction

As previously discussed, one problem with applying multivaraite analysis to neuroimaging data is the low number of subjects relative to the number of voxels. In included studies we therefore used the following strategies to reduce model complexity: In study I, only voxels with a mean positive beta value in the fMRI maps were used. While voxels with negative beta values, also called deactivations, may theoretically contain information about cognitive development, their importance and meaning is less well described and they were therefore excluded. For the other modalities all intracerebral voxels were used.

In study II a clustering algorithm was first applied to the DTI data in order to reduce the number of features(Ward et al., 1963). Neighboring voxels with a similar signal were clustered and treated like one feature. Secondly, these clusters were selected using univariate correlation with the outcome. Only clusters correlating over a set threshold were used when building the model. These two approaches reduced the number of features and thus the risk of over fitting the SVM models.

In study III, as partly the same datasets were used as in study I, the same strategy for the DTI, that is including all intracerebral voxels, was used.

Furthermore, in all studies only linear kernels were used in the SVM data fitting. This was to further minimize model complexity so over fitting could be minimized.

Smoothing

Smoothing of neuroimaging data is common prior to group based analysis in a standard anatomical space. This is partly done in order to accommodate for imperfections in the normalization process and reduce the physical measurement noise. In fMRI analysis it also accommodates for differences in functional anatomy. The smoothing commonly involves mathematical convolution of the data with a Gaussian function with a SD equal in all di-

mensions. This ensures equal smoothing in all dimensions in the case of anisotropic voxels. All studies in the current thesis use smoothing to some degree on the MRI data.

Cross validation

As previously discussed, cross validation is a good way of approximating model generalization on an independent sample when no such sample is available. In this thesis all studies used leave one out cross validation in order to acquire unbiased predictions of the outcome variables. Parameters for SVM models and feature selection were all set within each cross validation loop. The model predictions are thus completely independent of the training sample.

Support Vector Machines

SVM was used in all studies included in the thesis. After the feature selection the data from each subject was represented as a vector. These vectors was used as independent variables in the SVM model. As all studies used continuous outcome variables a regression adaptation of the SVM was used. The parameters in for the models were all determined in a nested cross validation loop. Only linear kernels were used to minimize model complexity.

General Linear Model analysis

In study I and II univariate analysis using GLM was used to correlate local MRI measures with cognitive development. Study I used the GLM analysis in order to provide some degree of localization of the prediction obtained by the SVM. This enabled the combination of the high prediction performance of the SVM with the localization ability and easy interpretation of the GLM. In Study II GLM analysis was used to explore univariate predictions between DTI and DBM on cognitive outcome.

3.5.3 Statistical Tests

Using the data processing and modeling described above, the analysis ultimately aimed to predict a variable of interest using the MRI data. The outcome variable was used as the dependent variable in the analysis. This variable is also frequently called label in computer

science literature. In study I, the variable of interest was score of a WM test two years after the MRI evaluation. Gray matter density measured with VBM, white matter microstructure measured with FA and neuronal activation measured with fMRI was entered separately into SVM models separately. The resulting predictions were combined using a linear multiple regression model. In study II the variable of interest was WM function or NA at the age of 5 and 7 years of age. This was predicted using multivariate models of FA and the DBM maps as well as univariate predictions with GLM. In study III the chronological age of the children in the developmental sample was the outcome variable used when training the SVM model. The model was applied to predict variability of chronological age in the cognitive training sample. This was to measure variability in brain development within a group of very narrow age range.

After obtaining cross validated predictions using the multivariate models the predictive ability was compared with that of other variables of interest. For study I this included WM measurements obtained at the same time as the MRI scanning in order to test the hypothesis of unique predictive ability of WM development. In study II the cognitive predictions were compared with those achieved from clinical factors gathered in the neonatal period. In study III we wanted to explore if variability in white matter development was independent of chronological age and therefore excluded it as a potential confounding factor.

In the GLM analysis for study I and II, confounding was controlled for by adding the possible confounders as independent variables in the GLM analysis.

Chapter 4

Results

4.1 Study I

4.1.1 Prediction of cognitive development

The SVM based regression models that were trained on VBM, DTI and fMRI to predict cognitive development two years after scanning all turned out significant, as assessed by correlation between the multivariate prediction of WM two years after MRI scanning and the measured WM score. DTI was the strongest predictor ($r = 0.59$, $p<0.001$) followed by fMRI ($r=0.44$, $p<0.001$) and VBM ($r = 0.29$, $p<0.05$). The predictions for the measures were combined in a multiple regression. This showed that only the DTI and the fMRI models explained unique variance . The DTI and the fMRI predictions retained significance for predicting WM capacity two years later , even when combined in the same model with a battery of cognitive tests conducted at the same time as the MRI examination (see figure 2). This indicated that information about future WM capacity that was not accessible using the cognitive test battery could be measured with MRI.

4.1.2 Localization of predictive effect

The multivariate prediction analysis had no spatial specificity, as the whole brain was included in the SVM model. We therefore proceeded with univariate exploratory analysis between the cognitive predictions and the MRI. Univariate analysis was done using GLM. The MRI based prediction of future WM function was entered as an independent variable in

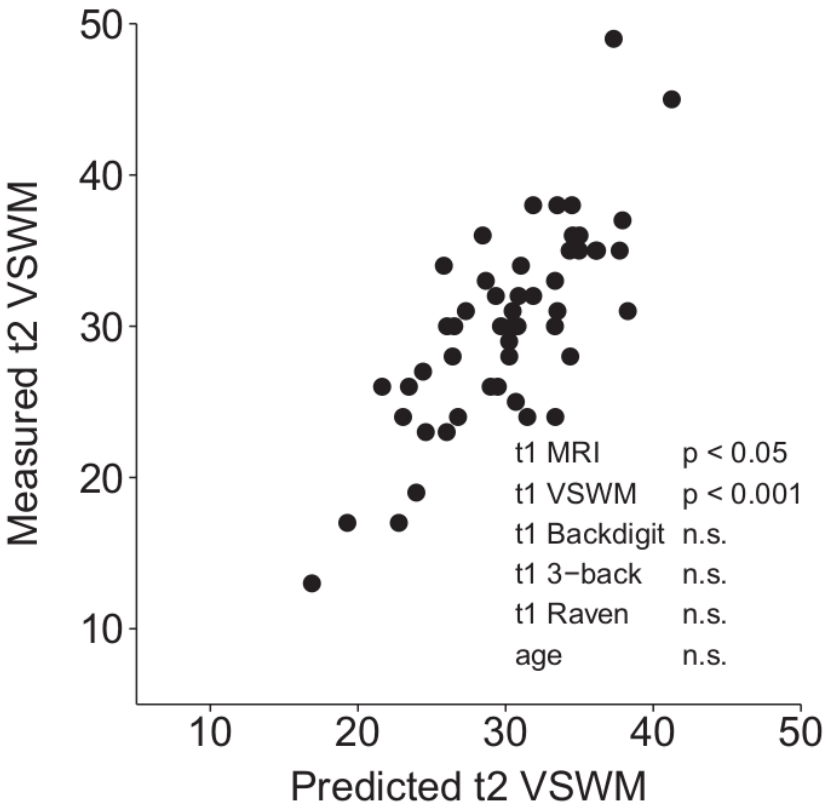

Figure 2: Scatter plot showing the prediction of Visuo-Spatial Working Memory (VSWM) two years after the MRI and baseline WM testing. The prediction from the MRI model was added together with VSWM and three other tests of WM and reasoning at baseline. Only the baseline MRI model and the baseline VSWM tests were significant ($p<0.05$) predictors of the follow up VSWM capacity.

the GLM model, together with concurrent WM capacity. The resulting univariate correlations thus indicate the unique predictive ability of the MRI based SVM model. This resulted in significant correlation with the fMRI signal in the basal ganglia and thalamus and FA correlation in the white matter regions surrounding these structures (FWE corrected $p<0.05$). The spatial distribution is shown in fig 3a. When correlating the concurrent WM capacity with fMRI a commonly reported correlative pattern of pre-frontal and parietal BOLD correlations was found. The regions showing correlation of concurrent WM capacity with fMRI BOLD signal are shown in figure 3c.

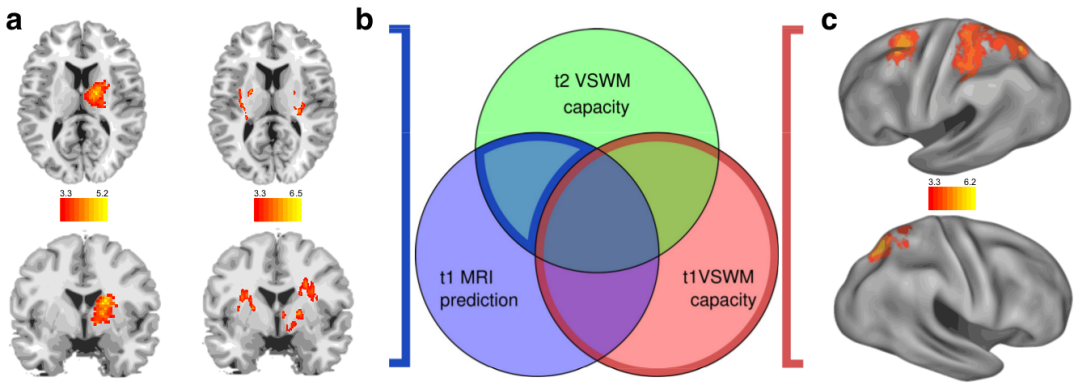

Figure 3: a) Maps showing the spatial locations of significant correlations between the multivariate prediction and BOLD signal.Functional MRI correlations are shown to the left and DTI correlations are shown to the right($p<0.05$, FWE corrected). b) Illustration of the shared and unique variance of concurrent Visuo-Spatial Working Memory (VSWM) and MRI prediction with future VSWM capacity. t1 indicates baseline measures and t2 indicates measures two years after the baseline. c)Correlations of concurrent VSWM capacity ($p<0.05$, FWE corrected).

4.2 Study II

Statistical analysis was conducted to predict WM and NA at 5 and 7 years of age. Two statistical approaches were used; a SVM based approach and a GLM based approach.

4.2.1 Prediction of WM development

DTI

The WM capacity at 5 years of age could be predicted from the neonatal DTI data using the SVM based analysis ($r = 0.36$, $p<0.001$). The GLM based analysis did not however show any significant clusters of correlation between the FA volumes and WM at 5 years of age. No significant SVM or GLM based predictions could be obtained for WM capacity at 7 years of age.

DBM

Correlations between increased tissue volume and WM capacity at 7 years of age were found in the left insula after correcting for gestational age at birth and gestational age at scan($p<0.05$). Similar trend effects were found at 5 years of age, but these did not reach significance($p = 0.07$).

4.2.2 Prediction of NA development

DTI

The NA at 5 years of age was predicted using the SVM model ($r = 0.35$, $p <0.001$). Similarly as WM, no significant prediction of NA at 7 years of age was obtained using the SVM analysis. GLM analysis failed to show any regions of correlation with NA at 5 or 7 years of age. Scatter plots of SVM predictions shown in figure 4.

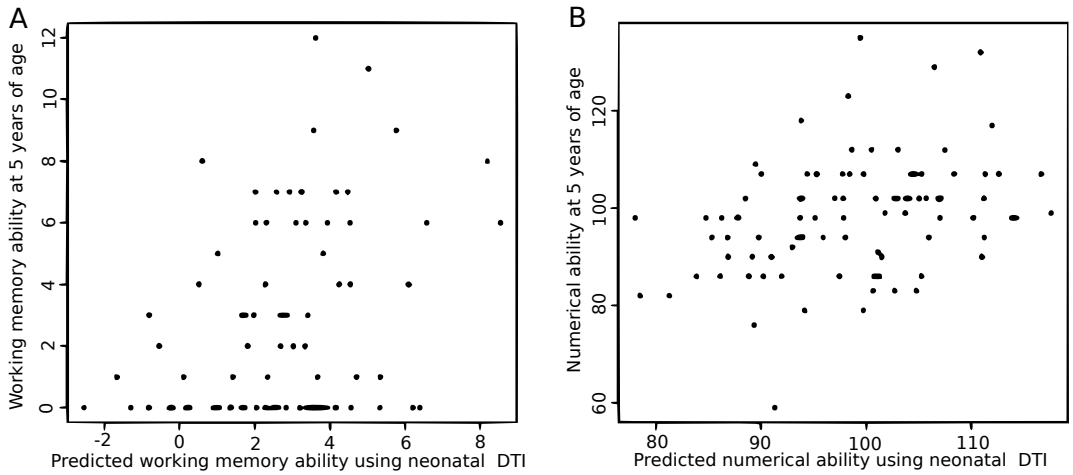

Figure 4: Scatter plots showing the predictive ability of the multivariate DTI model on a) WM capacity ($r = 0.36$, $p<0.001$) and b) numerical ability ($r = 0.35$, $p <0.001$).

DBM

The GLM analysis of the neonatal DBM maps showed regional correlations for both 5 and 7 years of age ($p<0.05$). These correlations were mainly localized to insular regions bilaterally. They also persisted after correcting for gestational age at birth and age at scanning. The spatial distribution of GLM correlations between DBM maps and NA is shown in figure 5

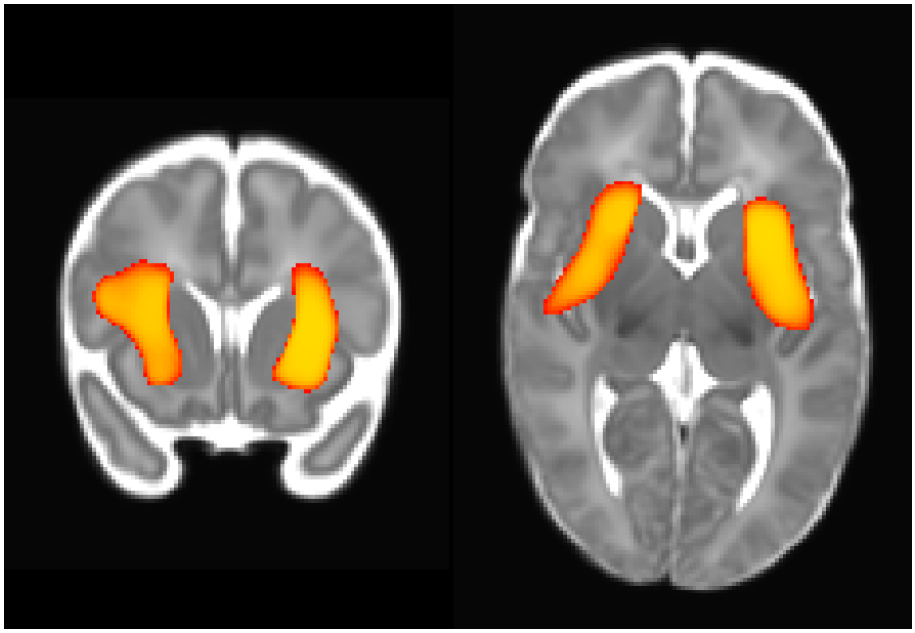

Figure 5: Distribution of correlations between the neonatal brain volumes and later numerical ability measured at 5 years of age (FDR-corrected p<0.05).

4.2.3 Comparison with clinical features

A secondary objective with the SVM analysis was to compare the obtained MRI predictions with previously known important factors in the neonatal period. The included factors were gestational age at birth, weather or not the children were small for gestational age, presence of patent ductus arteriosus, oxygen need at 36 weeks of age, administration of postnatal corticosteroids, presence of sepsis and and grading of the amount of lesions on the structural MRI according to a structured evaluation. The predictive ability of the DTI based SVM on WM and NA at 5 years of age was persistent after correcting for these factors, indicating that unique information could be obtained from the DTI.

4.3 Study III

The study explored two questions, the first was weather or not individual variation in maturation explains variability in cognitive abilities at school start. The second questions was weather this variability changes as the children grow up.

4.3.1 Modeling development

The SVM model of development was fit using the DTI from developmental sample. The trained model showed a high performance in predicting the chronological age in the sample (r=0.81, p<0.001). The scatter plot of the model is shown in figure 6. These results show that the model measured the level of brain maturation as measured with MRI. This was a necessary step in order to explore the relationship between maturation and cognitive function in school age children.

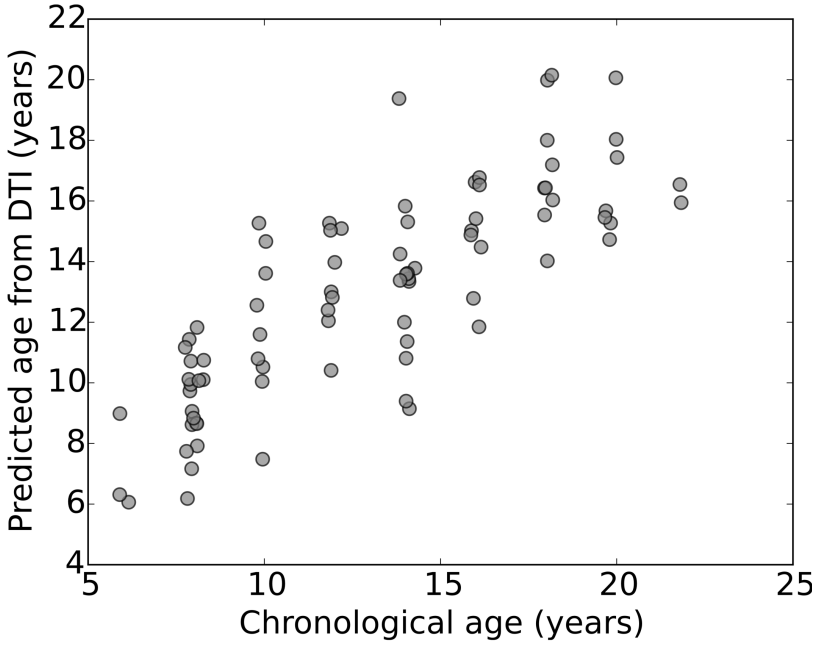

Figure 6: Scatter plot showing the performance of the multivariate model trained using the DTI from children to measure chronological age (r=0.81, p<0.001).

4.3.2 Chronological age and cognition in school entry age children

The model that was trained to predict chronological age in the developmental sample was applied to the baseline DTI data of the cognitive training sample. The predictions from the model indicated the level of brain maturation based on the FA maps. This FA based brain age was correlated with concurrent cognitive function in the children. The cognitive variables were latent WM and NA that were created using factor analysis. The FA based brain age

correlated positively with both the WM ($r = 0.50$, $p < 0.01$) and the NA ($r= 0.41$, $p<0.05$) variables. There was however no correlation between the WM or NA and chronological age ($p>0.5$), showing that the narrow age range of the group excluded the possibility of age as a confounder in this analysis.

4.3.3 The relationship between developmental variability and age

If the previously shown correlation between FA based brain maturation and cognitive function is due to variability in the individual time course of development a change over time can be predicted. As children grow older the rate of change in the developmental curves decrease. When reaching the asymptote, any differences in maturation that is due to variability in the individual time course are expected to have disappeared. This hypothesis was tested by comparing the correlation between FA based brain age and WM in the cognitive training and in the developmental samples. The developmental sample was divided using a median split at 13 years of age. The proportion of variance in WM explained by FA maturation decreased with age. In the cognitive training sample with the narrow age range of 6-7 years, the proportion was 52%. In the younger half of the developmental sample, aged 6-13 years the proportion was 16% and 8% in the older half of the sample (figure 7).

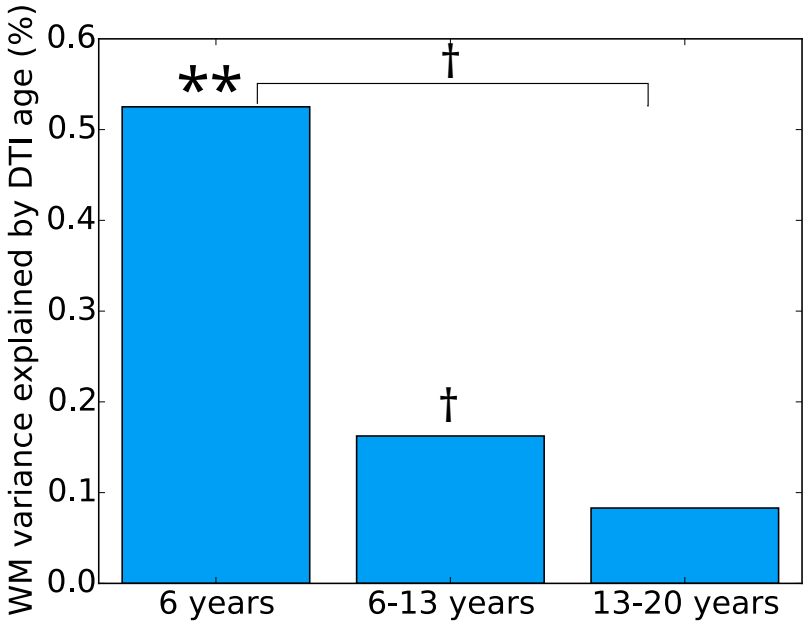

Figure 7: Illustration showing the proportion of WM explained by the variability in white matter maturation measured using the DTI model of development. In the youngest age group, 52% of the variance was explained by variability in white matter development. In the sample of children between 6 -13 years of age 16% was explained and in the group of children between 13-20 years of age only 8% was explained. ** indicated $p<0.01$, † indicates $p<0.1$.

Chapter 5

Discussion

5.1 Study I

In study I we showed that the future change in WM capacity could be predicted using structural and functional MRI and that this prediction contained information that could not be predicted by the battery of cognitive tests used concurrently. Further localizing analyses point towards a partly separate anatomical substrate of this prediction of the future and the concurrent WM function. The future development appeared to be more related to basal ganglia and thalamus while concurrent WM correlated with pre-frontal and parietal cortices (Klingberg et al., 2002; Kwon et al., 2002; Crone et al., 2006; Scherf et al., 2006; Geier et al., 2009; Jolles et al., 2011). The striatal selectivity for WM development has since been replicated and extended (Darki et al., 2015).

The results have impact for the clinical adaptation in cognitive neuroimaging where the prognosis of development often is of higher interest than the current developmental state. This study is therefore part of a growing body of work proposing cognitive predictions as a promising application of cognitive neuroimaging in clinical practice(Gabrieli et al., 2015).

It is important to consider that in order for cognitive predictions to be of clinical use they must change the clinical management. If no effective intervention is available cognitive predictions will only be interesting from an academic perspective. One can also argue that using cognitive predictions in normally developing children my promote a deterministic view of academic and work success. The results presented here show that while the predictions of WM development are significant they presently account for a small percentage of

the variance in later functioning. While the performance of the predictions probably will increase with technical and methodological advancements, there are no indications at present that cognitive predictions are of practical benefit in the healthy pediatric population.

Another point worth discussing related to Study I is how the uniqueness of the information from neuroimaging predictions relative to cognitive tests can be ascertained. Tests of higher order cognitive functions are noisy measures and their test retest reliability can often be increased by combining the results of multiple tests that measure the same cognitive facet. It is therefore hard to know if a neuroimaging prediction would still be significant given additional cognitive tests. In Study I we get the indication that the information is unique due to separate anatomical correlations between concurrent and future WM. From a statistical perspective however we can not fully exclude that an addition of further cognitive tests possibly combined with multivariate analysis would be able to replace the predictive abilities of the MRI.

5.2 Study II

The second study showed that WM and NA at school entry age could be predicted in the neonatal period using DTI. This analysis used DTI scans acquired at a term equivalent age as a substrate to a SVM with cognitive performance as the outcome variable. This dataset provided an opportunity to test the methods used in Study I on a clinical sample. The SVM model trained in Study I was not used in Study II due to the many differences in the datasets. Both the gross anatomy and the pattern of development show large differences between the ages of the samples. Because of this, SVM models were trained separately on the samples.

Using GLM analysis of volumetric DBM measures we could show some degree of anatomical specificity to the insular and basal ganglia regions.

The main implications of the results are that clinically useful variables, such as school age cognitive abilities could be predicted already in the neonatal period. There is an apparent use of these predictions to guide the use of cognitive interventions. While the association strength between the predictions and the actual outcome of Pearson correlation of 0.3 - 0.4 may be considered low to moderate, from a clinical perspective this is in the range of possible clinically relevant effect sizes. With a technological development that will likely continue to

increase the quality of MRI this predictive ability is also expected to increase.

To implement the results of the Study in clinical practice further analyses have to be done. These include studies of treatment effects if the cognitive predictions are followed by a cognitive intervention program. A study of the cost benefit should also be carried out. These analyses are out of the scope of the current thesis.

Lastly, prediction of cognitive functions is an estimate that contains a prediction error. When the correlation of predictive function and outcome is low there is a risk that more harm is done by stigmatizing children and parents. A prediction of low cognitive abilities may result in lower expectations and encouragement from parents and the school system, which may inhibit cognitive development.

One of the reasons the multivariate predictions using FA volumes may have worked well in the sample is due to the distributed and relatively consistent pattern of pathology. Patients where the pattern of imaging pathology is highly individual may not be well suited for automated analysis such as this. In Study II, children with significant focal lesions were excluded for this reason.

Other patient groups where a similar pattern analysis approach may prove useful are those with distributed pathology that has a similar distribution across patients but that may be difficult to accurately measure with conventional clinical reading of MRI scans.

5.3 Study III

In Study III we could show that WM and NA at school start correlated with a pattern of white matter development corresponding to normal chronological development. Furthermore, this correlation decreased as the children grew older, suggesting that the effect is transient and does not persist to a large degree into adulthood.

Variability in early physical development is a well known fact in clinical pediatrics and may not be predictive of the final developmental state. For example, the age of pubertal onset does not affect the final height in children with a normal puberty (Vizmanos et al., 2001). The age at reaching early developmental milestones is a bad predictor of adult cognitive functioning (Murray et al., 2014). Given the present results, similar features may be present in the development of the brain. As higher order cognitive functions develop late, this effect

may be present at the time children enter school. This has practical implications as children that have a later onset of cognitive development may be perceived of having persistent low cognitive function.

The results suggest a possible use of neuroimaging in tracking cognitive development. Neuroimaging would be able to function as a support to cognitive evaluations when differentiation between late developmental onset and persistent low cognitive function. At present, however the results for the study needs to be replicated further tested for clinical efficacy for the proposed use. Furthermore, additional studies are needed to further describe the anatomical differences between late developmental onset and persistent low cognitive function.

Chapter 6

Conclusions

The aim of the thesis was to show if and to what degree the development of cognitive functions, specifically WM, can be predicted in healthy developing children using MRI. We were able to show that a significant part of the variance in future WM capacity was predictable two years in advance by creating models using structural and functional MRI information. This study proved that information about cognitive development could be extracted from MRI in children that we could not easily evaluate from the used cognitive tests.

This result motivated us to take our findings to a clinical population, preterm born children, to explore if clinically useful predictions could be obtained using the technique. By using a similar approach, to predict cognitive function from MRI scans collected in the neonatal period we were able to show that clinically useful predictions regarding school age WM and numerical ability could be obtained.

These two studies together have implications for pre-clinical neuroscience as well as clinical psychology and medicine. From a pre-clinical neuroscience perspective the studies show that the developing brain can be seen as a reflection, not only of the current state of function but also of the future change. From the perspective of a practicing clinician within medicine or psychology the results are useful in that they show how cognitive neuroscience may be applied in the care of preterm born children.

Study III address an important question in neuroscience that is of relevance when predicting or correlating the variability in WM over development. The study shows that the variability in WM may correspond to different developmental mechanisms at different ages. A large part of the variability in young children may be due to developmental lags that largely

disappear with age. If children exhibiting transient developmental lags can be separated from children that run the risk of persistent cognitive deficits using MRI, resources for these last group of children could be better allocated.

These studies together illustrate the great usage and exciting possibilities that developmental cognitive neuroimaging may have on clinical practice and how further applications on clinical groups may inform basic neuroscience. Although the clinical applications proposed here must be seen as experimental and in need of further evaluation before put into clinical practice it is important to stress these possibilities in order to gain the interest of pre-clinical and clinical scientists. One of the determining factors of how much of the advanced neuroimaging of cognitive development will reach applications is the degree of shared interest between clinicians and neuroscientists in collaborating.

Chapter 7

Acknowledgements

Life does not turn out as expected for most people, including myself.
The theme of this this work is prediction of the future. This, in most areas suspect discipline, is what I have tried to bring some scientific credibility to in the developmental neuroscience field. It is very clear to me however that when it comes to real world accomplishments and how life turns out, most of the variance is driven by environmental, often seemingly stochastic events in the form of influence and help by individuals.
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Chapter 8

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