Chapter 9

General discussion, conclusions and future perspectives

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In this thesis, structural and functional MRI were used to investigate brain structure and function in 4-7 year old children born small for gestational age (SGA). The effect of postnatal catch-up growth on these parameters was investgated by comparing a group of SGA children with (SGA+) and without (SGA-) postnatal catch-up growth.

METHODOLOGICAL CONSIDERATIONS

Study population

SGA or IUGR?

In the current thesis, children born SGA were included to investigate effects of intra-uterine growth restriction (IUGR) on brain morphology and function. We used a stringent cut-off of birth weight and/ or birth length ≤ -2 SD to define SGA following the international SGA consensus conference, because with this definition the majority of children termed SGA have suffered from disordered fetal growth and the proportion of constitutionally small children will be minimal (Lee *et al.*, 2003). On the other hand, with this strategy, IUGR children with a birth weight and length above -2 SD are not included. (Mamelle *et al.*, 2001; Mamelle *et al.*, 2006). As already has been discussed in the general introduction and Chapter 3, inclusion based on serial ultrasound measurements during pregnancy would have been preferable from a methodological point of view. In the current study population, in the majority of SGA children (34/40) at least one ultrasound was performed. In 25/34 children prenatal growth restriction was suspected and confirmed with serial ultrasound investigations. In 9/34 children, no serial ultrasounds had been performed but 6/9 pregnancies were complicated with pregnancy-induced

hypertension or placental abnormalities, all likely to result in IUGR. In the remaining 6/40 children, no ultrasounds had been performed. Also, in these newborns, complications such as hypothermia or hypoglycaemia, suggestive for IUGR, were present.

In conclusion, despite our stringent cut-off, data from the antenatal ultrasound investigations indicate that only a very small fraction of our study population may not be SGA caused by IUGR but SGA due to other causes. A customized growth chart in the remainder of these children probably would have provided further insight whether these children indeed had suffered from IUGR rather than being constitutionally small.

Representativeness of the group of SGA children: gestational age
This study excluded children with a gestational age below 34 weeks. The majority of the children in this study were born at term (1 AGA, 2 SGA+ and 2 SGA- children were born at a gestational age below 37 weeks). Prematurity itself is an independent risk factor of inferior outcome in intelligence, cognition and altered brain architecture, and this risk increases substantially when gestational age is below 32 weeks (Chapter 3) (Peterson *et al.*, 2000; van Baar *et al.*, 2009). To be able to determine the effect of low birth weight on brain morphology and function, we excluded children with severe prematurity. Therefore, results of the current study cannot be extrapolated to children born prematurely.

Representativeness of the group of SGA children: parental education
The subgroup of SGA children in the current study project has an overrepresentation of highly educated families. According to the literature, parents from children born SGA have lower educational levels (Silva *et al.*, 2010; Auger *et al.*, 2008). In this particular SGA population, the percentage of parents reaching ≥ post-secondary education was approximately 45-50%. In the subgroup of SGA- children, this percentage was even higher: 55%. Because cognitive outcome is influenced by home environmental factors, among which parental educational levels, it may be expected that in SGA born children in families with lower parental educational levels the cognitive performance is lower than in our study group. Fortunately, there is also an advantage of the high parental educational levels of SGA group (see below).

Representativeness of the control group of AGA children
The group of AGA children in the current study project consisted of healthy children. Most of the children were friends or classmates of the SGA children; some were siblings, only a few control subjects were unrelated to the children. The mean IQ of the AGA children was almost 1 SD above the population mean. This raises the question whether this group is a representative test sample and we would like to add several comments to this issue. To exclude the possibility that most of the differences between AGA and SGA children are in fact caused by differences in IQ we performed several additional analyses.

First, we correlated IQ with all brain measures within each subgroup and did not find significant correlations. Second, we compared brain measures between low and high IQ groups within each subgroup (Chapter 5). None of the brain measures differed significantly between the low and high IQ groups. Third, significant differences between AGA and SGA groups remained significant after adjusting for IQ. Fourth, parental educational levels did not differ between the groups, indicating that the lower IQ in the SGA groups cannot be attributed to either parental (genetic) factors or the postnatal home environment (see previous section). In conclusion, we believe that the AGA group represents a good control group for this particular SGA population.

Study design

This thesis is part of a longitudinal study on effects of GH on brain development and cognition in children born SGA. One of the questions in the longitudinal study is whether GH treatment influences brain development, intelligence and cognitive outcome in SGA-children. For this purpose an untreated control group of SGA- children was planned in the study design. Unfortunately, during the inclusion period only one child was included in this group. After one year, this child switched to the treatment group. Those few SGA-children who were referred for short stature and finally decided not to be treated with GH did not want to participate. From the moment the consensus statement on SGA management was accepted, GH treatment became standard care and it was not possible to investigate the effect of GH treatment with a proper untreated SGA control group. For the studies described in this thesis, this was however not relevant because the children described in these studies were included before start of GH therapy.

NEUROIMAGING IN CHILDREN

Neuroimaging techniques and more specifically recent advances in functional neuroimaging techniques have enormously increased our knowledge on the functional organization of the brain during the last decades. The non-invasive nature (in contrast to more invasive techniques such as PET or SPECT) of functional MRI and MEG has permitted new investigations of brain-behaviour associations during both typical and atypical development. However, the use of these techniques in children remains a challenge due to ethical, practical and methodological considerations. Some of these have been discussed in the former chapters and will be highlighted in the following paragraphs.

Ethical aspects of scanning 4-7 year old children

In the Netherlands, ethical codes and regulations are formulated in The Dutch Medical research with Human Subjects Act (WMO, Ministry of Health Welfare and Sport, 1999).

These ethical codes are established in order to protect individuals against research risks and burdens, and ethical review committees review the ethical acceptability of research proposals. The Dutch Central Committee on Research involving Human Subjects (CCMO) supervises all ethical boards. Medical research can be divided into therapeutic and non-therapeutic research. In therapeutic research, investigators typically combine research with medical care and the research subjects can directly benefit from the study. In contrast, in non-therapeutic research, no direct benefit exists for research subjects who face the associated risks and burdens solely for research purposes. With respect to non-therapeutic research, the WMO is strictly guarding the upper limits of acceptable risks and burdens. Especially in children, the WMO prohibits non-therapeutic research with children unless 1. studies involve minimal risks and burdens (expected discomfort) 2. the study is group-related (i.e. cannot be performed with competent subjects) 3. during the study, expressions of objections of the subjects are respected.

The current study, being a non-therapeutic research project, was approved by the Medical Ethical Review committee of the VU University Medical Center after thorough consideration. The decision of the committee was formulated as follows: "this study meets all requirements according to article 4 WMO, because this study can only be performed with under aged participants and burdens are minimal".

By default, The Dutch Central Committee rejects all MRI studies involving children younger than 8 years old, mainly based on the assumption that in this particular age group minimal burden cannot be guaranteed. Subsequently, ethical boards tend to be very cautious in approving research protocols in pediatric populations unlike several other ethical boards, for instance ethical boards in the United States. However, since no clear definitions of minimal risks and minimal burdens exist, decisions to reject or approve research proposals ultimately depend on interpretation of individual ethical committees, as was the case in our study. Most studies investigating the burden of MRI procedures in pediatric populations focus on children above the age of 8 years. A recent study in 5-12 year old children undergoing a diagnostic MRI showed that MRI-related discomfort can be regarded as minimal in more than half of the children (Westra *et al.*, 2011). The authors did not find any evidence for the Dutch Central Committee's assumption that those children at risk for higher levels of discomfort can be identified solely by their age.

This study was not designed to investigate the degree of burden in 4-7 year old children undergoing MRI in a research setting and therefore cannot provide evidence for standard approval of future non-therapeutic research MRI studies. However, our personal observations during this study were unambiguously positive. Once children had completed the mock scanner protocol, the real MRI/ MEG procedure was performed without visible signs of distress. All children left the scanner rooms with excitement and joy.

We think that this study can serve as an example of a study in which optimal circumstances were created to guarantee minimal burden to each participant, and ethical rules as listed in the WMO are still adhered to. As such, this study might be of help in the current discussion on a more liberal attitude towards approval of non-therapeutic research in children while still adequately protecting individual subjects. Future studies should focus on the development and validation of age-appropriate questionnaires to ultimately assess the degree of burden in young pediatric research populations.

Practical aspects of scanning 4-7 year old children

Our studies have demonstrated that neuroimaging in children 4-7 years old is feasible. However, one should realize that many aspects of participating in an MRI or MEG experiment can be intimidating (large and noisy (MRI) machine, confinement in a narrow space). Together with a lack of comprehension, this may induce distress, resulting in poor or non-adherence and excessive movement. MRI scans and especially fMRI scans are highly sensitive to movement artefacts. Acclimation to the scanner environment and explanation of the scanning procedure are crucial to minimize these problems when scanning children. Our studies demonstrate that a mock MRI scanner training protocol is suitable to address the above listed issues and is effective in preparing young children to participate in MRI investigations. It enables investigators to select children for subsequent real MRI/fMRI procedure. Major conditions provided in the protocol are listed below:

For this study a staff of highly motivated and qualified (pediatric) psychologists, a lab assistant from the department of radiology and a pediatrician were present during all sessions allowing the child to be familiar with the staff in order to maximize each child's well being. Different sessions (neuropsychological testing, MEG and MRI) were on a separate day.

Parents or guardians of each child received extensive information by letter. Because 4-7 year old children do not understand the meaning and impact of this information, as an alternative, each child was given a DVD of the procedure. In this video, a 5-year-old child demonstrated all aspects of the procedure: the neuropsychological testing, MRI scanner environment, including scanning procedure and sounds, and MEG environment.

After the neuropsychological testing each child underwent a mock scanner training session as described in detail in Chapter 4 to acclimate the child to the future scanning procedure, assess the child's ability to remain still and to determine the child's ability to successfully complete the scanning procedure. If the training procedure could not be completed, children did not enter the real MRI procedure.

The sense of isolation of the child in the narrow bore was minimized by placing one of the parents/guardians and the pediatrician or psychologist next to the child during the actual MRI investigation, maintaining physical contact. Another staff member was

interacting with the child between runs from outside the scanning room through an intercom encouraging the child and checking whether a child was comfortable and ready to proceed.

Maximum effort was provided to place each child comfortably in the scanner with fitting earplugs and headphones, soft foam pads, comfortable button response devices and a favourite video to watch during structural scans.

Total scan procedure was kept to a minimum to minimize fatigue and boredom. Limited attention span is an important issue when scanning children. Whereas in adults scan protocol of 45 to 60 minutes are commonly used, total MRI scanning time in the current study was around 13 to 20 minutes depending on whether a child underwent resting state fMRI or not. In our opinion, maximum capacity increased with age and ranged from approximately 13 minutes in 4-5 years olds to 20 minutes in 6-7 years olds.

Based on the results of this study project, the use of the mock scanner has become a standard procedure in the VU University Medical Center to prepare pediatric patients for MRI procedures both in an in- and outpatient setting. It reduces the need for sedation in young children undergoing MRI. In children who are old enough to undergo an MRI without sedation a mock scanner training session can reduce preceding anxiety by exposing them in a step by step procedure to all aspects of an MRI investigation.

Methodological aspects of functional MRI in 4-7 years old children

Motion artefacts
Functional MRI is very sensitive to motion. Children move more than adults and, therefore, motion artefacts are a fundamental source of noise in pediatric fMRI studies. To correct for motion artefacts, motion correction is standard procedure in the post-processing of all fMRI data. Studies in adults demonstrate that the accuracy of motion correction algorithms decrease with increasing amount of motion (Ardekani *et al.*, 2001; Oakes *et al.*, 2005). Therefore, in adult fMRI studies, scans are usually excluded from the analysis when motion exceeds a certain level. A commonly used exclusion criterion in adults is when motion exceeds 2 mm. If the same strict criteria are used in young children it is not unlikely that the majority of children have to be excluded. Interestingly, for pediatric fMRI studies, no stringent criteria with respect to threshold for rejecting data due to motion exist. Some studies even do not report detailed information on the amount of motion (Byars *et al.*, 2002; Gathers *et al.*, 2004; Rivkin 2000). Other studies accept a more liberal threshold or exclude subjects based on visual inspection of the resulting statistical parametric maps rather than the amount of motion (Klaver *et al.*, 2008; Lichtensteiger *et al.*, 2008; Supekar *et al.*, 2009; Yerys *et al.*, 2009). A paucity of data on pediatric volunteers probably is at least partially an explanation. The question

remains whether it is justified to apply a more liberal threshold of motion in children, thereby tolerating suboptimal quality of scans. Currently, no methodological studies exist on comparison of fMRI motion correction algorithms in pediatric populations and future studies on this topic are necessary to standardize methodologies of pediatric fMRI analyses (Gaillard *et al.*, 2001).

BRAIN AND COGNITION IN SGA

Brain

SGA children have smaller brains with a disproportionately lower cerebral white matter volume (Chapter 5). In addition, cerebellar grey and white matter volumes are lower. Cerebral grey matter volume and hippocampal volumes are less compromised and comparable to AGA children, suggestive of relative sparing of these regions or compensatory growth postnatally. Regional differences in prefrontal cortical thickness suggest a different development of the cerebral cortex.

Animal studies on chronic placental insufficiency demonstrate that the brain, although relatively spared in relation to other organs (Morrison 2008), is reduced in weight and both grey and white matter are affected. IUGR animal models show lower white matter volumes with thinner myelin sheaths (Mallard *et al.*, 1998; Nitsos and Rees 1990; Duncan *et al.*, 2000). Neurons generally seem to survive but neuronal migration to the cortex can be delayed, dendritic and axonal outgrowth is retarded and synaptogenesis is compromised (Dieni and Rees 2003; Mallard *et al.*, 2000; Mallard *et al.*, 1998; Sasaki *et al.*, 2000). Reduced cortical thickness was found in sections of the temporal and occipital lobe, but no animal studies have investigated cortical thickness along the cortical mantle (Rees *et al.*, 1988). Although the nature and extent of the neuropathology varies in different IUGR models and is related to the severity of the insult and the timing and duration of the insult in relation to the gestational age, several studies suggest that IUGR during the last trimester specifically affects white matter rather than grey matter (Duncan *et al.*, 2000; Mallard *et al.*, 1998; Nitsos and Rees 1990). The predominant white matter differences described in this thesis is therefore in line with observations in animal models.

Few human studies exist on brain anatomy in children born SGA (Borradori-Tolsa *et al.*, 2004; Lodygensky *et al.*, 2008; Martinussen *et al.*, 2005; Martinussen *et al.*, 2009; Skranes *et al.*, 2005). In a cohort of term born SGA adolescents lower total brain volume was mainly caused by reduced white matter volume without significant differences in grey matter volume compared to healthy controls (Martinussen *et al.*, 2005; Martinussen *et al.*, 2009). A cohort of prematurely born SGA infants displayed lower total brain volume with lower cerebral cortical grey matter volume (Borradori-Tolsa *et al.*, 2004). These results are conflicting and suggest that, in line with animal studies, the nature and extent

of neuropathology (e.g. white vs. grey matter) depend on timing of the insult in relation to gestational age as well as on timing of study in relation to postnatal age.

The task-related fMRI study (Chapter 7) was developed to investigate long-term memory with specific interest in hippocampal function, because of its associated vulnerability in IUGR studies in animal models (Dieni and Rees 2003; Duncan *et al.*, 2004; Lister *et al.*, 2006; Mallard *et al.*, 2000; Lodygensky *et al.*, 2008). We found only very small differences in hippocampal volumes between AGA, SGA+ and SGA- children (Chapter 5). Furthermore, we found that the difference in encoding related activity between AGA and SGA children is only very subtle. SGA children demonstrate marginally lower parahippocampal activation without evidence for functional impairment of the hippocampus (Chapter 7). This finding contrasts with results of most animal and human studies which generally report reduced hippocampal volumes shortly after birth (Dieni and Rees 2003; Duncan *et al.*, 2004; Lister *et al.*, 2006; Mallard *et al.*, 2000; Lodygensky *et al.*, 2008). Interestingly, a more recent animal study investigated long-term effects of adverse prenatal conditions on brain structure in adult guinea pigs (Rehn *et al.*, 2004). This study demonstrated postnatal compensatory growth of the hippocampus from lower volumes after birth towards similar hippocampal volumes in adult guinea pigs. We hypothesize that shortly after birth, the brains of SGA children may be generally smaller than the brains of AGA children, but during development, catch-up growth takes place for selected areas, such as the hippocampus. In addition, specific cortical regions, such as the prefrontal cortex, have an aberrant developmental trajectory, leading to thicker prefrontal cortex. To test these hypotheses, human longitudinal studies are needed. In summary, based on previous literature, the focus of the task-related fMRI study was the hippocampus (Chapter 7). However, our structural MRI data indicate that differences in white matter volume and prefrontal cortex predominate in 4-7 year old term born SGA children. Therefore, the function of these brain regions should be the focus of future studies.

Cognition

Despite normal IQs, disadvantages of SGA children were seen across components of cognition, behaviour and in school progress. Already in the earliest stages of their academic career, twice as many SGA children repeated a grade at school, and needed more extra educational services or special education. In SGA- children disadvantages pertained to measures of learning and retention (memory). In SGA+ children, perceptual organization, visual memory and visuomotor integration were poor. SGA+ children have more behavioural problems than AGA and SGA- children. The combination of these organization and integration problems and the elevated level of behavioural problems in SGA+ fits our clinical impression of poor regulation in SGA+ children. In our sample, differences between the groups could not be ascribed to psychosocial factors.

Interplay between brain structure and function

Disadvantages in multiple components of cognition rather than impairments in certain isolated subtypes of cognition may occur in the setting of diffuse white matter abnormalities (Fields 2008; Fields 2010; Kumar and Cook 2002). Recently, differences in white matter structure have been correlated to individual differences in normal cognitive development, IQ, reading skills, working memory and musical proficiency (Fields 2008; Vernooij *et al.*, 2009). No direct relations were found between white matter parameters and neuropsychological test results (chapter 5 & unpublished observations). However, our group size was small and the differences observed with fMRI and neuropsychological testing were subtle. Therefore, the absence of an observed relation may not necessarily imply that such a relation does not exist and other neuropsychological tests and MRI-modalities should be used in the future (see below).

We recommend that future studies should focus on global connectivity of cortical networks. White matter tracts underlie structural connectivity between distinct cortical grey matter regions and, in general, strength of structural connectivity is positively correlated with functional connectivity strength within cortical networks (Damoiseaux and Greicius 2009; van den Heuvel *et al.*, 2009a). Because the white matter volumes in SGA children are significantly lower compared to those born AGA, we expect to find differences in structural connectivity between AGA and SGA children. For this purpose, diffusion tensor imaging (DTI) can be used to study micro structural changes within the cerebral white matter and the establishment of structural brain connectivity (Basser 1995). To investigate functional connectivity within cortical networks, MEG and functional connectivity MRI must be applied and subsequently analysed with graph analytic techniques to characterize the degree of connectivity within and between different cortical networks. Based on differences in white matter volumes and differences in regional cortical thickness we expect to find differences in functional connectivity of cortical networks in AGA compared to SGA. In the current thesis we already performed a pilot study and applied ICA rs-fc MRI to identify RSNs in 4-7 year old children.

The primary aim of the resting state functional connectivity MRI study described in Chapter 6 was to identify resting-state networks in 4-7 year old children in an awake state. This study was the first to demonstrate that networks previously identified in adults are present already at this young age (Chapter 6). Unfortunately, data of only 18 children (12 SGA+ and 6 AGA) were available for this study and therefore, only preliminary conclusions can be drawn from comparison between rather small subgroups of 6 AGA and 12 SGA+ children. Subgroup comparison between AGA and SGA+ children did not show significant differences in any of the resting state networks. However, there are several comments we would like to make. First, the lack of difference in the rs-fcMRI study may be caused by a low power because only 12 SGA+ and 6 AGA children were included. Second, recently developed techniques such as dual regression analysis or

graph analytic approaches can be applied to further characterize networks and to subsequently perform subgroup comparisons (Filippini *et al.*, 2009; Fair *et al.*, 2007; Fair *et al.*, 2008; Fair *et al.*, 2009). Third, our hypothesis was based on the assumption that white matter volume reflects structural connectivity. However, the difference in white matter volume does not automatically indicate different structural connectivity (Damoiseaux and Greicius 2009). To investigate this, future studies must apply additional techniques such as DTI in combination with rs-fc MRI (Olesen *et al.*, 2003).

An MEG study in this same group of children showed lower absolute power in SGA children suggestive for different synaptic density and lower synchronized neuronal activity, i.e. less connectivity within neuronal networks in the cerebral cortex (Boersma *et al.*, 2011). However, these MEG data should be interpreted with caution due to the small number of included children.

ANSWERS TO THE QUESTIONS FORMULATED IN THE INTRODUCTION

Can a mock scanner training protocol be used for preparing young children for magnetic resonance imaging in a research setting? (Chapter 4)

Yes, the use of a mock scanner training protocol results in a high percentage of successfully conducted MRI scans in both research and diagnostic setting.

Does brain structure differ in (4-7 year old) SGA children in comparison with children born AGA? (Chapter 5)

Yes. Children born SGA have smaller brains with lower cerebral and cerebellar white matter volumes and smaller cortical surface area. Most obvious was a smaller cortical white matter volume in SGA children. Regions of thicker cortex were most pronounced in the medial prefrontal cortex bilaterally, but also concerned discrete regions within the posterior cingulate cortex and superior parietal cortex.

Does brain function differ in (4-7 year old) SGA children in comparison with children born AGA? (Chapter 6, 7)

Yes, brain function differs in SGA but only very subtly as measured with the current neuroimaging methods/paradigm. The focus of the task-related fMRI study (Chapter 7) was restricted to long-term memory function with specific attention to the process of visual encoding. Based on chapter 7, we can conclude that the neural substrate of visual encoding in SGA children is comparable to AGA with only minor differences to the disadvantage of SGA. In the rs-fc-MRI study we did not observe a difference between SGA and AGA children.

Do intelligence, cognitive functioning and behaviour differ in (4-7 year old) SGA children compared to AGA children? (Chapter 8)

SGA children demonstrate intelligence levels in the normal range but lower than AGA children. Although SGA children do not have statistically significant poorer scores on the different measures of cognition and behaviour than do AGA controls, standardized performances are nearly all to the disadvantage of the SGA children. Already in the earliest stages of their academic career, twice as many SGA children repeated a grade at school, and needed more extra educational services or special education.

Do SGA+ and SGA- children differ with respect to brain structure, function and intelligence & cognition? (Chapter 5, 7, 8)

Yes, in some respects, SGA+ children constitute an intermediate between SGA- and AGA. This was most obvious in the structural MRI study. Bodily catch-up growth in children born SGA does not implicate full catch-up growth of the brain structure and function. With respect to intelligence and working memory, SGA+ constitute an intermediate between AGA and SGA-. For the other cognitive domains, this trend was not present. In SGA+ children, disadvantages are mainly restricted to imperfections of self-regulation and behavioural performance, whereas SGA- children remain behind on measures of learning and retention.

SUGGESTIONS FOR FUTURE STUDIES

- standardization of methodologies to analyse pediatric MRI data.
- structural connectivity of white matter in SGA and AGA children with DTI.
- animal models investigating white matter and cortical thickness along the cortical mantle with specific attention to the prefrontal cortex.
- task-related fMRI focused on the prefrontal cortex.
- the characterization of functional connectivity within and between cortical networks (rs-fc MRI, rs-MEG).
- neuropsychological testing focused on the function of the prefrontal cortex.
- assessments of self-regulation to study executive aspects of responses apart from established levels of skill or attainment, and apart from the clinical surroundings of test laboratories.
- the natural course of the differences in brain structure, brain function and neuropsychology between AGA and SGA+ children (current study project).
- the effect of growth hormone treatment on differences in brain structure, brain function and neuropsychology in SGA- children (current study project).