Effects of preterm birth:

Associations between brain volumes, neuropsychological functioning, and side preference in school age children.

Nina Bask
Anna Bäckström
Först och mest vill vi tacka alla barn och föräldrar som så givmilt delat med sig av sin tid, ställt upp så att vi fick öva och som försökspersoner. Utan er hade denna uppsats aldrig blivit.

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A preterm birth is associated with increased risk for neurocognitive deficits, but there is a need to further investigate brain/behavior relations among younger school age children born preterm. The main purpose of this study was to investigate relations between brain volumes and neuropsychological functioning, with an additional aim of examining side preference, among 18 school age children, nine born extremely/very preterm and nine born at-term. Brain volumes were examined using 3T MRI, neuropsychological functioning by WISC-IV and side preference through laterality observations. The children born preterm had, in general lower total brain volume, gray matter and WISC-IV score. Contrary to previous findings no difference was found regarding white matter volumes. Stronger right hand preference was associated to higher perceptual reasoning ability among both preterm and at-term born children, but the associations between right hand preference and brain volumes differed between the groups. The results in this study support previous findings showing long-term neurocognitive effects of a preterm birth.


The number of surviving preterm born children has increased in the last decades, mainly because of improvements in neonatal care (Behrman & Butler, 2007). In Sweden, about 5% of all newborn children are born preterm. A minor part (≈1%) is extremely/very preterm (≤27/28-32 weeks) whilst the major part (≈ 4%) is late preterm (33-35 weeks) (The National Board of Health and Welfare, 2013). Gestational age is strongly associated with birth weight and children born preterm often has very low or low birth weight (VLBW 1000-1500 gram; LBW 1500-2500 gram) (Behrman & Butler, 2007).

Children born preterm have an increased risk for adverse developmental outcomes, such as cerebral palsy, intellectual disability, visual- and auditory impairments where the children born extremely/very preterm are the most afflicted (Allen, 2008; Behrman & Butler, 2007; Bhatta, Cleves, Casey, Cradock, & Anand, 2002). However resent studies have also described increased risk, even among children born late preterm, for more subtle neurodevelopmental
impairments such as neuropsychological and motor impairments (Baron, Litman, Ahronovich, & Baker, 2012; Soria-Pastor, et al., 2009).

The increased risk for adverse developmental outcomes among children born preterm is well established in the literature. However, there is a lack of studies concerning how different pre- and postnatal risk factors contribute to the neurodevelopment, how the development progresses and the transient or permanent nature of the deficits (Allen, 2008; Aylward, 2005; Mento & Bisiacchi, 2012). It is important to find more specific predictors for adverse developmental outcomes. This, not only because it enables the children to get the right kind of treatment but also because it is essential in order to evaluate treatments. Furthermore, more individualized risk assessment assists healthcare personal to give better support and advice to the families.

Cognitive function and brain development among children born preterm
Infants have already at birth cognitive abilities that enable their adaption to the prenatal environment (Rönnqvist & Hofsten, 1994). They can to some degree orient and focus their attention and comprehend visual stimuli such as familiar faces. They can also recognize voices and make pitch discrimination, abilities that support later language development (Mento & Bisiacchi, 2012). These cognitive abilities are underpinned by the development of the brain that takes place prenatally. Disruption of this process has in many cases been shown to alter both the structural organization of the brain and cognitive development among infants born preterm (Baron, et al., 2012; Mento & Bisiacchi, 2012; Peterson, et al., 2003).

Alteration of brain development and cognitive functioning has been shown among both younger and older children born preterm in comparison to age typical development. The alterations of the brain can be seen both globally and locally. Lowered brain volumes, gray matter (GM) volumes and white matter (WM) volumes are found among seven to 18 year old children born very preterm (de Kieviet, Zoetebier, van Elburg, Vermeulen, & Oosterlaan, 2012). Reductions and alterations of brain volumes and GM/WM volumes (Baron, et al., 2012) as well as local cerebellar reductions (van Soelen, et al., 2010) are also found among children born late preterm. A recent meta-analysis (de Kieviet, et al, 2012) shows that the more specific reductions described in the literature is not significantly different from the global reductions. This suggests that the reductions in brain volume is fairly equally spread across the brain regions studied. This result however is not confirmed by a study regarding regional specific alterations (Peterson, et al., 2000).

Associations between brain alterations and cognitive function among children born preterm and with LBW have been shown in several studies (de Kieviet, et al., 2012). Lowered intellectual functioning has been associated with lowered total brain volume among eight year old children born preterm (Peterson, et al., 2000). It has also been associated with WM reductions (Northam, Liégeois, Chong, S Wyatt, & Baldeweg, 2011; Taylor, Filipek, Juranek, Bangert, Minich, & Hack, 2011) and cerebellar WM reductions (Taylor, et al., 2011) among adolescents born
preterm. Lowered intellectual functioning has furthermore been associated with lower GM volumes subcortically among adolescents (Taylor, et al., 2011) or in temporal and parietal regions among nine year old children (Soria-Pastor, et al., 2009) born preterm. More specific cognitive impairment such as language, executive functioning, visuo-spatial and perceptual impairments has also been associated with both global and more specific brain alterations among adolescents born preterm (Taylor, et al., 2011). Higher executive functioning has also been associated with higher total brain volume and cerebellar volume among five year old children born preterm (Lind, et al., 2010).

**Hand/side preference and neurodevelopment among children born preterm**

A clear preference of hand has been found already among young children (Rönnqvist & Domellöf, 2006). Among school age children about 90% of the population manifests a right hand preference (Szaflarski, et al., 2012). However, among children born preterm elevated numbers of non-right handedness have been found and the results indicate that a shorter prenatal period can lead to higher ratios of non-right handedness even in those cases where no developmental deviation is present (Burdukova & Stroganova, 2008; Domellöf, Johansson, & Rönnqvist, 2011).

The adult brain has normally a distinct side difference in reference to both function and anatomy (Szaflarski, et al., 2012) and these anatomic side differences are founded early, starting already in the third trimester (Baron, et al., 2012). It is not fully established in which way a preterm birth effects the specialization of the brain but a suggestion is that the higher proportion of non-right handedness among children born preterm is associated with an atypical or disturbed development of cerebral asymmetry (Domellöf, et al., 2011). However, the results among different studies regarding the associations between handedness and cerebral asymmetries are diverse and conflicting. Some studies have shown a relation between non-right handedness and atypical brain specialization, especially in relation to functional language asymmetries, both in preterm populations (Myers, et al., 2010) and in other non-right handed populations (Szaflarski, et al., 2002). Other studies in preterm populations have failed to find any associations between non-right handedness and atypical brain specialization (Kesler, et al., 2006; Lancefield, et al, 2006).

Both hand preference (Marlow, Hennessy, Bracewell, & Wolke, 2007) and brain asymmetry (Myers, et al., 2010) have been associated to neuropsychological functioning. Non-right handedness is associated with increased risk for rightwards laterality or a less pronounced leftwards bias for language and it is suggested that when language and spatial functions are located to the same hemisphere there will be deficit in cognitive ability (Powell, Kemp, & García-Finaña, 2012). Some studies presents’ evidence that non-right handedness associates to various neuropsychological outcomes such as lower general intelligence quotient (IQ) (Marlow, et al., 2007; Powell, et al., 2012), decreases in working memory capacity and verbal comprehension (Powell, et al., 2012) as well as perceptual function (Marlow, et al., 2007; Powell, et al., 2012). Other studies fail to show any

Since there are few findings regarding the brain/behavior relations among younger school age children born preterm (de Kieviet, et al., 2012) and conflicting results regarding the associations between handedness, brain alterations and neuropsychological functioning among preterm born children (Domellöf, et al., 2011), the aim of this study was two-fold.

The main purpose was to examine brain volumes, neuropsychological functioning and the relationship between these among younger school age children born preterm in comparison to children at the same age born at-term. An additional aim was to assess hand/side preference among the children and the relations between non-right hand/side preference, neuropsychological functioning and brain volumes.

Based on previous findings we hypothesized lowered total brain volumes among the children born preterm as well as lowered GM and WM volumes, even after total brain volume correction. Lowered neuropsychological functioning was also expected among the preterm born children, both in general intelligence as well as for verbal comprehension, working memory and perceptual functioning. Another assumption was to find associations between brain volumes and neuropsychological functioning.

Method

Participants
The children participating in this study consisted of a subsample selected from an ongoing study at the department of Psychology, Umeå University (PI: Professor L. Rönnqvist). All the preterm born children were at birth cared for at the neonatal intensive care unit at Norrlands University Hospital (NUS) in Umeå, Sweden. Of the sixteen selected extremely/very preterm born children, seven was missing the magnetic resonance imaging (MRI) data needed for participation and was excluded from the study sample. A control group was selected from the at-term born children participating in the ongoing study. Selection criteria’s for the at-term born children was used in an attempt to match the children born preterm considering age at participation and sex. The final study sample consisted of nine extremely/very preterm born children and nine children born at-term, seven girls and two boys in each group. Information about the participating children regarding age at participation, neonatal data and parental education is presented in Table 1.
Table 1. **Demographic and neonatal data.**

<table>
<thead>
<tr>
<th></th>
<th>Preterm (n=9)</th>
<th>At-term (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>8.1 (1.0)</td>
<td>8.1 (0.8)</td>
</tr>
<tr>
<td><strong>GA (weeks)</strong></td>
<td>29.0 (2.2)</td>
<td>40.4 (1.1)</td>
</tr>
<tr>
<td><strong>BW (grams)</strong></td>
<td>1109 (365)</td>
<td>3587 (288)</td>
</tr>
<tr>
<td><strong>Apgar 5</strong></td>
<td>7.9 (1.7)*</td>
<td>9.1 (0.3)</td>
</tr>
<tr>
<td><strong>Apgar 10</strong></td>
<td>9.0 (0.8)*</td>
<td>9.6 (0.5)</td>
</tr>
<tr>
<td><strong>Mothers education (years)</strong></td>
<td>13.8 (3.4)</td>
<td>13.6 (1.7)</td>
</tr>
<tr>
<td><strong>Fathers education (years)</strong></td>
<td>12.7 (2.4)</td>
<td>13.4 (2.1)</td>
</tr>
</tbody>
</table>

Note: n = number of subjects; M = mean; SD = standard deviation; GA = gestational age; BW = birth weight; * = one subject missing data.

**Apparatus and material**

**Wechsler’s Intelligence Scale for Children**

Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) (Wechsler, 2003) is a widely used instrument that assesses neuropsychological functions in children 6-16 years-at-age, both in research and clinical practice. Cognitive ability is assessed in four domains, verbal comprehension (VCI), perceptual reasoning (PRI), working memory (WMI) and processing speed (PSI). These indexes are summed up in a full-scale intelligence quotient (FSIQ), which is a measurement of general intelligence. The assessments in this study included the ten core subtest of the Swedish version of WISC-IV (Wechsler, 2007). If the child did not qualify for the core subtest Letter-number sequencing, nine core subtests and the supplementary subtest Arithmetic were used.

**Assessment of hand/side preference**

In order to assess side preference of the hand, foot/leg and eye, a laterality instrument was used. This instrument is based on two laterality questionnaires, Edinburgh Handedness Inventory (Oldfield, 1971) and the Measurement of laterality (Coren & Porac, 1980). The instrument consists of different tasks, five performed with the hand, three with the foot/leg, and one with the eye, all repeated five times. Side preference was assessed by observing if the child chose to use left or right hand, leg/foot or eye. The measurement of hand preference consisted of the observations of the hand only. Based on the observations a laterality index was calculated (r-l/r+l) with the values ranging from 1 to -1. In accordance with earlier studies (Stefanis, et al., 2006) a value below .3 represents a non-right preference.

**Synthetic MR**

Brain scans where obtained through the use of 3-Tesla magnetic resonance imaging (MRI) and a relatively new technique, synthetic MRI (SyMRI)
(SyntheticMR, Linköping, Sweden, www.syntheticmr.com) was used in this study for processing the MRI data. This technique uses data of T1-relaxation, T2-relaxation and proton density to estimate tissue parameters per voxel and create SyMRI images (see figure 1 for example images). In this study, the software SyMRI Brain Studio (SyMRI diagnostics beta 2 release 2) was used to estimate brain volumes of intra cranial volume (ICV), brain parenchymal volumes (BPV) (consisting of WM, GM and other non-specific matter), GM, WM and cerebrospinal fluid (CSF). SyMRI brain studio also estimates the relative BPV, GM, WM, and CSF volume by calculating their respective percent of total ICV. SyMRI has been shown to give reliable measures of brain volumes (Ambarki, et al., 2012). The estimations of brain volumes was made in the newest version of SyMRI Brain Studio but due to technical reasons prepared in the previous release of SyMRI Brain Studio. An automated-corrected method was used to define the ICV. The software SyMRI Brain Studio detected the border between bone and CSF, which constitutes the ICV border. Two trained operators manually corrected the ICV on T2 weighted synthetic images with an experienced radiologist as a reference. A correlation of a sub sample (six preterm and two at term born children) showed a high accordance ($r=.99$) between the tissue estimates produced by the trained operators and the experienced radiologist.

![Figure 1. Example images. T1 weighted SyMRI images showing from left to right, WM in blue, GM in green, and CSF in pink.](image)

**Study design**

In order to study effects of a preterm birth a case-control study design was used.

**Procedure**

In the study the children’s cognitive functioning was assessed as well as their motor functions and side preference. Questionnaires regarding the children’s medical status and information about family demographic were also administrated. The children's cognitive functioning was assessed with WISC-IV during two blocks in a quiet room with little distracting material in it. The subtests of WISC-IV were administrated in the order stipulated in the WISC-IV manual (Weschler, 2003) with a short break in the middle. The children participating in the study was allowed to become acquainted with the MRI scanning procedure in a
realistic camera model at Umeå University, before undergoing an approximately 30 minutes long MRI scan at NUS.

**Statistical analysis**
The hand/side preference data was analyzed by use of Chi-square test, Pearson’s and Spearman’s correlations (due to non-normal distributions). The outcomes regarding neuropsychological functioning and brain volumes were analyzed using Pearson’s correlations and analysis of variance (ANOVA). All statistical analyzes was conducted in IBM SPSS statistics version 21 with the confidence interval fixed at 95% and the α-level at 0.05.

**Ethical considerations**
This master thesis is based on an ongoing study investigating effects of a preterm birth, approved by Umeå Regional Ethical Board (Dnr 05-104M ). The children that participate in the study and their parents were informed about the purpose of the study and all the parents of the participating children gave written informed consent.
Results

**Brain volumes**
The assessment of brain volumes among the preterm and at-term born children showed that the at-term born children had significantly larger ICV, BPV and GM volumes as well as relative GM volume (see table 2). One preterm born child had WM volume regarded as an extreme outlier (>3 interquartile range) in the sample however no significant difference was found for WM even when this child's data was excluded.

Table 2. Brain volume data.

<table>
<thead>
<tr>
<th>Brain volume</th>
<th>Preterm (n=9)</th>
<th>At-term (n=9)</th>
<th>F (df)</th>
<th>p value</th>
<th>η²ρ</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICV ml</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>4.76 (1,16)</td>
<td>.044</td>
<td>.229</td>
</tr>
<tr>
<td>BPV ml</td>
<td>1310 (89)</td>
<td>1416 (116)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM ml</td>
<td>1131 (88)</td>
<td>1237 (96)</td>
<td>5.91 (1,16)</td>
<td>.027</td>
<td>.270</td>
</tr>
<tr>
<td>WM ml</td>
<td>642 (49)</td>
<td>740 (64)</td>
<td>13.43 (1,16)</td>
<td>.002</td>
<td>.456</td>
</tr>
<tr>
<td></td>
<td>429 (42)</td>
<td>437 (51)</td>
<td>0.13 (1,16)</td>
<td>.724</td>
<td>.008</td>
</tr>
<tr>
<td></td>
<td>416a (19a)</td>
<td>1.15 (1,15)a</td>
<td>.301a</td>
<td>.071a</td>
<td></td>
</tr>
<tr>
<td>CSF ml</td>
<td>178 (28)</td>
<td>179 (36)</td>
<td>0.00 (1,16)</td>
<td>.963</td>
<td>.000</td>
</tr>
<tr>
<td>BPV (RV)</td>
<td>86.4 (2.2)</td>
<td>87.4 (2.0)</td>
<td>1.15 (1,16)</td>
<td>.299</td>
<td>.067</td>
</tr>
<tr>
<td>GM (RV)</td>
<td>49.0 (2.5)</td>
<td>52.3 (2.2)</td>
<td>8.38 (1,16)</td>
<td>.011</td>
<td>.344</td>
</tr>
<tr>
<td>WM (RV)</td>
<td>32.8 (2.3)</td>
<td>30.8 (2.5)</td>
<td>2.86 (1,16)</td>
<td>.110</td>
<td>.152</td>
</tr>
<tr>
<td>CSF (RV)</td>
<td>13.6 (2.2)</td>
<td>12.6 (2.0)</td>
<td>1.15 (1,16)</td>
<td>.299</td>
<td>.067</td>
</tr>
</tbody>
</table>

Note: M = mean; SD = standard deviation; df = degrees of freedom; p value = significance value, significant values are bold; η²ρ = partial eta square; ICV = intra cranial volume; BPV = brain parenchymal volume; GM = gray matter; WM = white matter; CSF = cerebrospinal fluid; ml = milliliter; (RV) = relative volume; a= exclusion of one extreme outlier.

**Neuropsychological functioning**
A difference was found between the children born preterm and at-term regarding neuropsychological functioning. The at-term born children had significantly higher FSIQ score and WMI score in comparison to the preterm born children (see table 3 for differences between the groups).
Table 3. Neuropsychological data.

<table>
<thead>
<tr>
<th>WISC-IV</th>
<th>Preterm (n=9)</th>
<th>At-term (n=9)</th>
<th>F (df)</th>
<th>p value</th>
<th>η²</th>
<th>ρ</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSIQ</td>
<td>92.7 (10.7)</td>
<td>105.9 (9.6)</td>
<td>7.67 (1,16)</td>
<td>.014</td>
<td>.324</td>
<td></td>
</tr>
<tr>
<td>VCI</td>
<td>93.3 (11.6)</td>
<td>104.0 (12.4)</td>
<td>3.58 (1,16)</td>
<td>.077</td>
<td>.183</td>
<td></td>
</tr>
<tr>
<td>PRI</td>
<td>97.9 (15.0)</td>
<td>108.3 (10.1)</td>
<td>2.99 (1,16)</td>
<td>.103</td>
<td>.158</td>
<td></td>
</tr>
<tr>
<td>WMI</td>
<td>87.4 (8.6)</td>
<td>98.8 (13.0)</td>
<td>4.77 (1,16)</td>
<td>.044</td>
<td>.230</td>
<td></td>
</tr>
<tr>
<td>PSI</td>
<td>96.9 (14.4)</td>
<td>104.7 (9.0)</td>
<td>1.88 (1,16)</td>
<td>.189</td>
<td>.105</td>
<td></td>
</tr>
</tbody>
</table>

Note: M = mean; SD = standard deviation; df = degrees of freedom; p value = significance value; significant values are bold; η² = partial eta square; n = number of subjects; WISC-IV = Wechsler Intelligence Scale for Children, 4th edition; FSIQ = full scale intelligence quotient; VCI = verbal comprehension index; PRI = perceptual reasoning index; WMI = working memory index; PSI = processing speed index.

Associations between brain volumes and neuropsychological functioning

Analyzes of associations between brain volumes and neuropsychological functioning were conducted among the children born preterm and at-term respectively. Among the children born preterm, a significant correlation was found between higher PRI score and larger ICV ($r = .679, p = .044$) and for higher PSI score and larger WM volume ($r = .797, p = .010$) and relative WM volume ($r = .685, p = .042$). Among the children born at-term, higher score of FSIQ ($r = -.737, p = .028$), VCI ($r = -.715, p = .030$) and WMI ($r = -.730, p = .026$) was significantly correlated with lower relative GM volume (see figure 2 for an illustration of the correlation between FSIQ and relative GM volume).

Figure 2. Correlations between FSIQ scores and relative GM volume.
Possible associations were further investigated between birth weight, brain volumes and neuropsychological functioning in the two groups respectively. No significant correlation between birth weight, brain volumes and neuropsychological functioning were found among the children born preterm. There was however a significant correlation between greater birth weight and larger WM volumes \((r=.889 \; p=.001)\) and relative WM volumes \((r=.668, \; p=.049)\) among the children born at-term.

**Hand/side preference**

In this sample, 89% of the preterm born and 100% of the at-term born children was classified as being right handed. After examination of side preference, 56% of the preterm born and 67% of the at-term born children was classified as having a right side preference (see table 4). No significant difference between the preterm and the at-term born children regarding handedness \((\chi^2(1)= 1.06, \; p>.05)\) or side preference \((\chi^2(1)=0.23, \; p>.05)\) was found.

**Table 4. Laterality index and laterality categorization data.**

<table>
<thead>
<tr>
<th>Hand preference</th>
<th>Side preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>M (SD)</td>
<td>RH (n)</td>
</tr>
<tr>
<td>Preterm (n=9)</td>
<td>0.71 (0.21)</td>
</tr>
<tr>
<td>At-term (n=9)</td>
<td>0.86 (0.12)</td>
</tr>
</tbody>
</table>

*Note: M = mean; SD = standard deviation; RH = right handed; NRH = non-right handed; RP = right side preference; NRP = non-right side preference; n = number of subjects.*

No significant associations were found between strength of right side preference and neuropsychological outcomes or brain volumes neither among the children born preterm or at-term. There was however a significant correlation between stronger right hand preference and higher PRI, among both the children born preterm \((r_s =.761, \; p = .017)\) and at-term \((r_s =.736, \; p = .024)\). Stronger right hand preference was also significantly correlated with larger GM volume \((r_s =.723, \; p = .028)\), larger BPV \((r_s =.672, \; p = .047)\) and larger ICV \((r_s =.714, \; p = .031)\) among the preterm born children. In contrast, a significant correlation was found among the at-term born children between stronger right hand preference and higher relative WM volume \((r_s =.832, \; p = .005)\).

**Summary**

Assessments were made of brain volumes, neuropsychological functioning and hand/side preference among the children. The results showed that the at-term born children had significantly larger GM volumes, BPV and ICV as well as higher FSIQ score and WMI score. No significant difference was found for WM volumes, even when controlling for an extreme outlier. Stronger right hand preference was associated with higher PRI scores among both preterm and at-term born children.
as well as with larger ICV, BPV and GM volumes among the children born preterm and larger relative WM volume among the at-term born children.

Discussion

The main purposes of this study were to examine brain volumes, neuropsychological functioning and its associations among children born preterm in comparison to children born at-term. An additional aim was to investigate hand and side preference among the children and associations between hand/side preference, brain volumes and neuropsychological functioning. The findings showed lowered brain volumes and neuropsychological functioning among the children born preterm. This indicates that being preterm born still, at school age, have effects on the children's general intelligence, working memory functions and GM volumes. Additionally, the strength of right hand preference seems to be associated with different brain mechanisms within the two groups of children. Nonetheless evident right hand preference seems to be an indicator of higher perceptual functioning among both preterm and at-term born children.

Brain findings

As expected, the preterm born children in this study had lowered ICV and BPV. The hypothesis of lowered GM and WM volumes however was partly confirmed where only GM volume differed significantly between the groups. These findings are not in line with previous results where both WM and GM volumes are found to be lowered among preterm born children (de Kieviet, et al., 2012). Previous research however has studied brain volumes mainly among adolescents born preterm and there is a lack of studies focusing on younger children born preterm. These somewhat contradicting results pinpoint the importance of examining intra and inter individual differences when studying alterations in brain development among preterm born children. The findings in this study may indicate a lack of knowledge regarding the developmental pattern of WM at different ages among children born preterm.

Studies of brain development among children show that there is an age specific increase and decrease in brain volumes as a part of age typical development. GM volumes increase in a region depending fashion until around the beginning of adolescences when it starts to decrease (Giedd, et al, 1999). In contrast, WM volumes show a steady increase until the end of the adolescences (Paus, et al., 2001). This age typical development has been shown to be altered among preterm born children. A longitudinal study, between the age of eight and 12, have shown that preterm born children have less decrease of GM and a lower increase of WM over time in comparison to children born at-term (Ment, et al., 2009). Furthermore have developmental patterns of WM been shown to differ between the sexes. The age typical development of WM has been shown to be steeper among boys than girls (Giedd, et al., 1999). WM volumes have also been shown to differ significantly between preterm and at-term born boys but not girls at young school age (Reiss, et al., 2004). The results from the present study shows that a continued focus on intra
and individual differences are needed when studying developmental patterns of the brain and possible brain alterations.

**Neuropsychological findings**

The hypothesis of lower neuropsychological functioning among the preterm born children was partly confirmed by the data analyses, where general intelligence and working memory was significantly lowered. The WMI difference wasn’t the only contribution to the lowered FSIQ score since the preterm born children had generally lowered means in all WISC-IV indexes although non-significant. This however does not mean that the preterm born children in this sample had overall cognitive deficits. In this study, the children born at-term had means that were higher than the norm populations on all indexes except for WMI. Furthermore, the index means of the preterm born children did not differ more than ½ standard deviation from the WISC-IV population norms, with the exception of WMI. Comparing the single indexes, only the WMI was significantly lowered among the children born preterm with a mean score of WMI almost one standard deviation lower than the population norm of WISC-IV. Index score that differ this much from the population norm mean is regarded to be of clinical value (Flanagan & Kaufman, 2009). Even though, the findings among preterm born children regarding lowered general neuropsychological functioning might be of clinical value in a sample with another kind of background. The parents of the participating children born preterm showed a high level of education and parental education and socioeconomic status has been shown to associate with cognitive functioning among preterm born children (Sommerfelt, Ellertsen, & Markestad, 1995).

**Brain volumes and neuropsychological outcomes**

Examining neuropsychological functioning and brain volumes, an association was found among at-term born children between lower relative GM volume and higher FSIQ score as well as VCI and WMI score. This association was not found among the preterm born children. The children born at-term showed a GM volume pattern that could be interpreted as an association between cortical thinning and higher IQ and working memory function whilst this pattern was not displayed among the preterm born children. Preterm birth was associated with lower IQ and WMI scores and lowered volumes of GM. These results are in line with previous research (Shaw, et al., 2006) showing that higher IQ is associated with earlier cortical thickening and later cortical thinning.

Associations were also found between higher ICV and larger PRI score as well as larger WM volume, relative WM volume and higher PSI score among the preterm born children. This shows an association between larger brain and higher perceptual functioning among the preterm born children, indicating that ICV is playing a part in perceptual functioning. However, the high perceptual scores among the preterm born children show that this association is of less clinical relevance, which might be a result of improvements in neonatal care. The association between advances in process speed and increasing WM volumes was only shown among the preterm born children. This might be due to a delay or
bigger developmental differences in this group and a more homogenous process speed development among children born at-term.

The relation between greater birth weight and larger WM volume among the children born at-term may be a finding in line with previous research. A linear association has previously been shown between WM volume and gestational age (Nosarti, et al., 2008) which is strongly associating with BW. However, this finding needs to be investigated further since this association generally is shown among preterm born children and not among children born at-term.

**Hand/side preference**

The assessment of hand and side preference among the preterm and at-term born children showed no significant difference regarding the prevalence of non-right side preference and non-right handedness. These results are not in line with the results of earlier research where significantly larger incidences of non-right handedness were found among preterm born children (Burdukova & Stroganova, 2008; Domellöf, et al., 2011). The small sample size of this study may have an effect on these results and it is possible that a difference would have been displayed with a larger sample.

In the present study, stronger right hand preference associated to higher PRI score among both the preterm and at-term born children. The effect of motor abilities on these results are most likely small since no significant associations was shown for PSI, an index highly effected by motor abilities. This suggests that the association between a less pronounced right hand preference and a lower PRI score is linked to perceptual capacities rather than to motor difficulties. These results are in accordance with previous research also showing associations between non-right handedness and lower perceptual functioning (Marlow, et al., 2007; Powell, et al., 2012).

An association was found between stronger right hand preference and larger GM volumes, BPV and ICV among the preterm born children. Earlier research suggests that a non-right handedness among children born preterm may depend on an interruption or alteration of the expected development of the brain (Domellöf, et al., 2011). Further did ICV, BPV and GM differ significantly between the preterm and at-term born children in this study. This might indicate that a less pronounced right hand preference among children born preterm may be associated to alterations in brain volumes. Stronger right hand preference was among the children born at-term in contrast associated to higher relative WM volume in this study. Among the at-term born children, right hand preference seems to be a sign of differences in brain maturation and possibly side specialization. These findings are in line with previous results showing that age typical brain maturation can be seen both in a cerebral specialization and in a more pronounced handedness (Coren & Halpern, 1991). The relation between brain, neuropsychological functioning and handedness needs further investigation. Even tough, non-evident hand preference shows a potential to be an indicator for perceptual developmental
delays and/or deviation as well as lowered brain volumes among preterm born children.

No significant association was found in this study between brain volumes, neuropsychological outcome and side preference. Previous research (Coren & Porac, 1980) has shown low correlation between foot, eye and hand assessment suggesting that factors affecting for example handedness may not affect other lateral preferences. These results give a possible explanation to why no significant association was displayed in this study.

Limitations to be considered
First, a larger study sample would have given more power to the analysis and improved generalizability. It is possible that associations and differences in the results are omitted due to the small sample size and inherent variability. Further, it is also possible that differences and associations are unrepresentative to the population of preterm born children due to the large contribution of each participating child. Nevertheless, findings of significant differences and associations in line with the hypothesis in such a small sample show that the focus of this study holds relevance for future research and clinical practice. Another limitation is that the number of statistical analyzes made on the data have affected the risk of type I error. A $\alpha$-level was set at 0.05 and some of the results in our study are significant at a near 0.05 level making them more afflicted by the higher risk of random effects that the many analyzes have contributed to. Still, the effect sizes of the findings are over all large which indicate a strong relation between preterm birth and lowered brain volumes and neuropsychological functioning. (Howell, 2007)

Second, the brain volumes in this study were assessed using a relatively new technique, SyMRI. Due to the novelty of this technique, interpretation of the brain data should be done with some caution since the validation of this technique is still in progress (Ambarki, et al., 2012; Vågberg, et al., 2013). Nevertheless, this study is showing that the technique seems to be of valuable use in the assessment of brain volumes among preterm and at-term born children as the results regarding differences and associations generally are in line with previous research. It is a promising technique especially for research regarding children. Brain scanning methods demand quite much of its participants and are very challenging for many younger children (Carter, Greer, Gray, & Ware, 2010). Many ethical issues have to be considered regarding participation, such as how big a challenge the MRI examination is for the child and if there is enough clinical value for the child to do a MRI under anesthesia. SyMRI is shown to shorten the time in the camera (Vågberg, et al., 2013), an important aspect of clinical brain research among children.

Additionally, a preterm birth is most often accompanied by birth complications such as different infections and respiratory problems, so also in this study. This means that casual relationships can’t be established since shown effects can be caused by the complications associated with preterm birth. The preterm born children in this study however have no current neuropathology, which makes a
more homogenous sample, reducing the bias possibly effecting the relation between preterm birth and lowered brain volumes and neuropsychological functioning. However, conclusions of developmental delay and deviation are best driven from a longitudinal design.

**Future research**

Earlier research has showed executive functioning to be an area affected by a preterm birth (Aarnoudse-Moens, Weisgias-Kuperus, Van Goudoever, & Oosterlaan, 2009), and that a lowered functioning in this area may affect the performance on other cognitive performances (Marlow, et al., 2007). The assessment in this study included only working memory as evaluating a part of executive functioning (Miyake, et al., 2000). Since WMI was the only cognitive index where a significant difference was found between the groups, it is possible that executive functions are an area in a larger extant affected by a preterm birth. Inclusion of more specific tests measuring this area of functions would be of interest in future research in order to get a more wide understanding of the effect a preterm birth have on executive functions and the relations between brain and behavior.

The brain shows a rapid functional specialization during the school years and this is also shown in the growing amounts of WM (Jernigan, et al., 2011). The development of stronger connections between functional brain networks can be understood as an interactive process between experience and brain maturation (Johnson, 2010). Among preterm born children, this brain maturation is taking place in what seems to be a differently developed brain, and experiences are in many cases made with less developed neuropsychological functioning, especially lower working memory ability. Research has showed that children born preterm now days have a lower risk for adverse cognitive developmental outcomes compared to children born preterm a few decades ago (Baron & Rey-Casserly, 2010). This shows the importance of studying the development of these children to be able to compare the long-term outcome of different treatment strategies. Longitudinal studies are eligible in this research area since it is important to understand the development and the intra and inter individual differences. The treatments given at birth to preterm born infants mediate various of the adverse effects of a preterm birth but there are still a need for strategies that more sufficiently protects and supports brain maturation and cognitive development. There might be interventions given at different stages during the development that could mediate adverse developmental effects. To find risk indicators are central to assist future treatment development. It is important to further investigate how the neuropsychological and brain development progress among these children and if treatment, training and coping strategies can mediate the differences in comparison to the at-term born children.

**Conclusion**

In line with previous research this study supports findings that a preterm birth has implications later in life. Being preterm born was at early school age associated with lowered ICV, BPV and GM volume as well as lowered neuropsychological
functioning with working memory as the area most affected. No difference was found for WM volumes, a result somewhat contradicting to some previous findings. This indicates need of knowledge regarding the developmental patterns of WM among younger children born preterm. This study found an association between stronger right hand preference and higher perceptual ability. Stronger right hand preference was also associating with larger ICV, BPV and GM volume among preterm born children. Associations were in contrast found with higher relative WM volume among the children born at-term. These relations need further investigation but non-evident hand preference shows a potential to be a risk indicator for perceptual developmental delays and/or deviation and lowered brain volumes among preterm born children.

References


