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Visual-motor integration and fine motor skills in children born extremely preterm: associations with neonatal brain volumes

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Manuscripts

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3 **Visual-motor integration and fine motor skills in children born extremely**
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5 **preterm: associations with neonatal brain volumes**
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Abstract

Objectives

This exploratory study aimed to investigate associations between neonatal brain volumes and visual-motor integration (VMI) and fine motor skills in children born EPT when they reached 6.5 years of age.

Setting

Prospective population-based cohort study in Stockholm, Sweden, during three years.

Participants

All children born before gestational age 27 weeks 2004-2007 in Stockholm, without major morbidities and impairments, and who underwent magnetic resonance imaging at term-equivalent age.

Main outcome measures

Brain volumes were calculated using morphometric analyses in regions known to be involved in VMI and fine motor functions. VMI was assessed with The Beery-Buktenica Developmental Test of Visual-Motor Integration - Sixth Edition and fine motor skills were assessed with the manual dexterity subtest from the Movement Assessment Battery for Children-Second Edition, at 6.5 years. Associations between the brain volumes and VMI and fine motor skills were evaluated using partial correlation, adjusted for total cerebral parenchyma and sex.

Results

Out of 107 children born at gestational age <27 weeks, 83 were assessed at 6.5 years and 66/83 were without major brain lesions or cerebral palsy and included in the analyses. A representative subsample underwent morphometric analyses: automatic segmentation (n=34) and atlas-based segmentation (n=26). The precentral

gyrus was associated with both VMI ($r=0.54$, $p=0.007$) and fine motor skills ($r=0.54$, $p=0.01$). Associations were also seen between fine motor skills and the volume of the cerebellum ($r=0.42$, $p=0.02$), brainstem ($r=0.47$, $p=0.008$) and grey matter ($r=-0.38$, $p=0.04$).

Conclusions

Neonatal brain volumes in areas known to be involved in VMI and fine motor skills were associated with scores for these two functions when children born EPT without major brain lesions or cerebral palsy were evaluated at 6.5 years of age. Establishing clear associations between early brain volume alterations and later VMI and/or fine motor skills could make early interventions possible.

Strengths and limitations of this study

- This was a robust population-based cohort study design that used advanced magnetic resonance imaging techniques and established assessment tools
- It studied visual-motor integration and fine motor skills in extremely preterm born children at 6.5 years, which is an important age for Swedish school children
- Although we had to exclude numerous children from the morphometric analyses, due to strict data quality criteria, the sample was representative of the cohort
- We were unable to include a control group of children born at term in the analyses

Funding

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Competing interests: None

Introduction

Visual-motor function is an important cross-modal ability that involves the integration of visual function and perception, eye-hand coordination, fine motor skills and visual-motor integration (VMI) ¹. Studies have shown that VMI can predict a child's future hand-writing skills ²⁻⁴ and academic performance in reading, writing and mathematics ⁵. Evaluating VMI performance is therefore an important component of the test batteries that are used to detect children who risk school problems. Fine motor skills are a fundamental component of hand and visual-motor function, which also

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3 contributes to school performance⁶. Several reports have shown that children born
4 preterm have poor VMI and motor function^{7 8-10} and it is well known that this group of
5 children risk poor school performance and learning disabilities¹¹⁻¹³.
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10 Although problems with VMI can stem from any of the underlying abilities listed
11 above, when VMI and motor abilities have been investigated together, and
12 perceptual and general cognitive abilities have been held constant, children with
13 lower general motor scores are seen to have lower VMI scores¹⁴. Children born very
14 low birth weight show a similar pattern¹⁵: VMI showing stronger relationships with
15 motor ability than with visual perception, suggesting that motor skills and manual fine
16 motor skills in particular, are crucial components underlying VMI. On the other hand,
17 visual perceptual deficits in children born EPT are well documented⁷ and their role in
18 VMI should not be underestimated. Therefore, an inductive exploration of brain
19 areas associated with VMI is a useful approach, especially when investigating
20 potentially atypical brain development trajectories¹⁶.
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34 It is largely unknown how the developmental alterations of the brain affect VMI and
35 fine motor skills in children born preterm. However, we have previously reported that
36 neonatal brain volumes are affected in preterm infants¹⁷, and other researchers have
37 shown that these alterations in preterm brain volumes persist until at least early
38 childhood¹⁸. Volumetric alterations in the brain have also been associated with
39 neurodevelopmental outcomes in preterm born children^{19 20}. However, the
40 relationship between volume alterations in the brains of children born extremely
41 (EPT), at less than 27 weeks of gestation, and VMI and fine motor skills at school
42 age remains largely unexplored. We hypothesized that early brain volume alterations
43 would be related to later VMI and fine motor skills in such children. To explore these
44 possible associations, we used atlas-based and automatic segmentation to measure
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3 the brain volumes at term-equivalent age, and carried out a clinical evaluation of VMI
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5 and fine motor skills at the age of 6.5 years.
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7 8 **Methods**

9 10 ***Study population***

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12 The study population was a sub-cohort of the Extremely Preterm Infants in Sweden
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14 Study (EXPRESS) cohort. EXPRESS was a prospective national population-based
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16 cohort study which invited all children born in Sweden at a gestational age (GA) of
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18 less than 27 weeks over a three-year period to take part in clinical follow ups at 2.5
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20 and 6.5 years of age^{21 22}. The present study included 107 children born in Stockholm
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22 between January 1 2004 and March 31 2007, without chromosomal aberrations,
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24 congenital malformations or infections, who had undergone magnetic resonance
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26 imaging (MRI) of the brain at term equivalent age.
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29 Gestational age was assessed by maternal ultrasound at around a GA of 18 weeks
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31 and perinatal and neonatal data were prospectively collected from the children's
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33 medical records. Cranial ultrasound was performed on a regular basis during the
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35 neonatal period up to a GA of 40 weeks, according to our clinical routine. Children
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37 were excluded from the analyses in the present study if they had major brain lesions
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39 defined as intraventricular hemorrhage, periventricular leukomalacia, severe white
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41 matter score according to Inder²³ or hydrocephalus, or cerebral palsy (CP) as
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43 defined by the Surveillance of Cerebral Palsy in Europe Working Group²⁴. All
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45 children had been screened for retinopathy of prematurity and evidence-based
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47 treatment had been administered²⁵.
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51 The study was approved by the local ethics committee in Stockholm and the parents
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53 of all the children gave their written, informed consent before the study.
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56 ***Assessment at 6.5 years of age***

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3 Visual-motor integration was assessed using the Beery-Buktenica Developmental
4 Test of Visual-Motor Integration - sixth edition ²⁶. This test consists of 30 geometrical
5 shapes that the child is asked to copy with a pen and paper and it is terminated when
6 three figures in a row have been incorrectly copied. The drawings are examined and
7 acceptable approximations of the model drawings are each given one point. The raw
8 score is the total number of correct drawings and this is then transformed to an age-
9 corrected standard score. Standard scores were used in the analyses in this study.
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11 The normative mean score is 100 with a standard deviation (SD) of 15.
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15 Fine motor skills were assessed with the manual dexterity subtest of the Movement
16 Assessment Battery for Children – Second edition (M-ABC-2) which measures
17 unimanual speed, bimanual coordination and unimanual spatial accuracy ²⁷. Age-
18 adjusted standard scores were used for the analyses. The reference mean score is
19 10 with a standard deviation of 3, and scores below 7 indicate definitive or borderline
20 motor problems.
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24 Binocular visual acuity was measured with habitual correction at three meters with
25 the Lea Hyvärinen chart ²⁸. Visual impairment was defined as a visual acuity of less
26 than 0.33 in the better eye.
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33 ***MRI data acquisition and processing***

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35 All the children were scanned using a Philips Intera 1.5 Tesla MRI system (Philips
36 International, Amsterdam, The Netherlands) at term equivalent age. A sagittal T1-
37 weighted turbo spin echo sequence, an axial inversion recovery sequence and an
38 axial T2-weighted sequence were run. The three-dimensional T1-weighted images
39 were acquired with an echo time of 4.6 msec, a repetition time of 40 msec, a flip
40 angle of 30°, a voxel size of 0.7 × 0.7 × 0.1 mm and a field of view of 180mm. The
41 MRI protocol has previously been reported ²⁹. Quality assurance was considered
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3 important in order to obtain accurate data, even though this meant that we were left
4 with a relatively small sample size. The imaging data was checked for quality, based
5 on a visual inspection of the raw data sets, and the reasons for low imaging quality
6 are presented in **Figure 1**.
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10 11 12 ***Atlas based segmentation*** 13

14 The brain was divided into 90 anatomical regions, by adapting an automated
15 anatomical labelling neonatal atlas³⁰, as previously described¹⁷. Briefly, the intensity
16 image that generated the neonatal atlas was registered to the T1-weighted image of
17 each infant, then the generated deformation field was used to transform the label
18 map with 90 regions from the atlas space to the subject space. A visual inspection
19 was performed for each subject and each step.
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27 We selected brain regions that had been previously described as being in the
28 networks that mediate VMI and fine motor skills, namely the visual, salience, sensory
29 motor and default mode networks³¹⁻³³. We also considered the subcortical regions:
30 pallidum, putamen, caudate and thalamus. The volume of each brain region was
31 determined by adding together the volumes of their components.
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39 ***Automatic segmentation*** 40

41 We first performed automatic segmentation of brain tissues (T1-weighted images)
42 using SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm>), running on MATLAB version
43 7.5 (MathWorks, Natick, Massachusetts, USA). This process focused on specific
44 neonatal priors, including grey matter, white matter, cerebrospinal fluid, deep grey
45 matter, the cerebellum and brainstem, which have previously been described in detail
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34³⁵. We then applied a Diffeomorphic Anatomical Registration Through an
Exponential Lie algebra algorithm (DARTEL) to improve the inter-subject registration
³⁶. Finally, all the images were modulated. The Easy Volume Toolbox³⁷ was used to

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3 extract the global brain tissue volumes from the segmented, normalized and
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5 modulated images of each child.
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8 ***Statistical analyses***

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10 The analyses were carried out with SPSS for Windows, version 22.0 (SPSS Inc,
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12 Chicago, Illinois, USA) and the data were checked for normality, homogeneity and
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14 outliers. In order to compare the groups, we used the Student's t-test and Mann
15
16 Whitney U test for continuous variables and the chi-square test or Fisher's exact test
17
18 for categorical data, as appropriate. The associations between brain volumes, VMI
19
20 scores and fine motor skills scores were explored using partial correlation. Total
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22 cerebral parenchyma (CPAR) – the sum of the grey matter and white matter,
23
24 excluding cerebrospinal fluid - was used as a covariate to control for generalized
25
26 scaling effects. Because sex, GA at birth and the GA at the time of the scan have
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28 previously been shown to influence brain volume size in preterm children^{38 39} we
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30 performed the analyses with different covariate pairs. First we used CPAR and GA at
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32 birth, then we used CPAR and the GA at scan and finally we used CPAR and sex.
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34 GA at birth and GA at scan did not influence the results, but sex did, so CPAR and
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36 sex were chosen as the covariates in the final model. There was one multivariate
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38 outlier which was identified by the Mahalanobis distance when we investigated the
39
40 atlas segmentation data in relation to the fine motor skills scores, and this child was
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42 excluded from those analyses. Bonferroni's correction for multiple comparisons was
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44 not applied because of the exploratory nature of the study and the reduced sample
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46 size examined⁴⁰⁻⁴². The level of significance was set at a two-sided p-value of <0.05.
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53 **Results**

54 ***Study population***

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3 A summary of the study population is presented in **Figure 1** and their perinatal
4 characteristics are presented in **Table 1**. At the time of the scan, the median (range)
5 GA in the 66 children without major brain lesions or CP was 40.8 (39.1-45.3) weeks
6 and for the assessment of VMI and fine motor skills it was 6 years 5 months (6 years
7 3 months - 7 years 2 months).

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13 The subsample of 34 children with high-quality MRI scans was representative of the
14 whole cohort with regard to their perinatal and neonatal characteristics, findings on
15 structural MRI, gestational age at MRI, age at assessment at 6.5 years and mean
16 VMI and fine motor score (**Supplementary Table 1**). During the atlas-based
17 segmentation process, 8 subjects had co-registration failure, leaving 26 children in
18 the final sample. These 26 children were also representative of the cohort of 66
19 children with regard to the above characteristics, except for days on mechanical
20 ventilation, which was a median (range) of 3 (0-36) days for the sub-sample versus
21 10 (0-55) days for the other children ($p=0.04$) (**Supplementary Table 2**).

32 33 34 35 ***Assessment at 6.5 years of age***

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37 The mean (SD) VMI standard score for the 66 children without major brain lesions or
38 CP was 93 (10), 7 points (0.5 SD) below the norm. The mean (SD) VMI scores for
39 the 29 girls was higher than for the 37 boys: mean (SD) at 96 (10) versus 90 (8),
40 respectively ($p=0.02$).

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46 The mean (SD) fine motor skills score was 8 (3), which was 2 points (0.5 SD) below
47 the norm, and there were no significant sex differences as the girls scored 8 (3) and
48 the boys 7 (3) ($p=0.16$).

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None of the children included in the study had a visual impairment.

Brain volumes and associations with VMI and fine motor skills

We identified a number of regions that demonstrated significant associations between brain volumes, VMI and fine motor skills scores. VMI performance showed a positive correlation with the volume of the precentral gyrus (partial $r=0.54$, $p=0.007$), whereas the fine motor skills scores showed a positive correlation with the volumes of the precentral gyrus (partial $r = 0.54$, $p=0.01$), the cerebellum (partial $r = 0.42$, $p=0.02$) and the brainstem (partial $r = 0.47$ $p=0.008$) and a negative correlation with cortical grey matter volume (partial $r = -0.38$, $p=0.04$) (**Figure 2**). All the correlation analyses can be found in **Supplementary Table 3**.

Discussion

In this study, the associations between brain volumes at term equivalent age and VMI and fine motor skills at 6.5 years in children born EPT without major brain lesions or CP were explored in regions of the brain previously reported to be involved in those functions. The volume of the precentral gyrus showed a positive correlation with both VMI and fine motor skills, and the volumes of the cerebellum and the brainstem correlated positively to fine motor skills. Total cortical grey matter volume showed a negative correlation with fine motor skills.

The group scores for the children included in this study were below the test norms on both VMI and fine motor skills, which was in line with previous studies where children born preterm have consistently shown poorer VMI performance and fine motor skills compared to children born at term^{7 43}. However, the lower group performance is still considered to be within low average range. Within this relatively well-functioning group of children born EPT, we found a small, but statistically significant, difference between the sexes with regards to VMI performance, with girls outperforming boys. Sex differences in VMI performance have consistently been reported in children born

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3 preterm⁷ and MRI studies of children born preterm have revealed differences
4 between the sexes in brain volumes and the microstructure of the brain^{38 44 45},
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6 indicating altered early development of the brain in boys born preterm. This indicates
7 that the brain of preterm born boys develops in an altered way compared to preterm
8 born girls, affecting both the structure and the function of the brain.
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14 Cerebellar underdevelopment, with reductions in cerebellar volume, and sustained
15 white matter injuries in children born preterm, have been suggested as possible
16 mechanisms for poor visuo-motor function^{46 9 33}, although many neural networks
17 comprised of other neural structures have also been proposed to be involved in VMI
18 including the visual, motor, sensory, salience and default mode networks, the
19 subcortical regions and the brain stem^{47 48}. Even though this study is the first, to our
20 knowledge, to explore the associations between brain volumes at term equivalent
21 age and VMI at 6.5 years in a cohort of children born EPT, there have been previous
22 reports of associations between brain volumes and VMI performance in more mature
23 preterm children. In these reports, positive correlations were seen between the
24 growth rate of the caudate and the thalamus during the neonatal period and VMI
25 scores at 4 years of age³¹, and between thalamic and cerebellar white matter
26 volumes and VMI scores at 15 years of age³². We did not find these associations in
27 our cohort and this finding was in line with a previous study that evaluated 8-year-old
28 children born preterm⁴⁹. One explanation for these different results could be
29 individual childhood growth trajectories and different gestational ages in the various
30 study cohorts. Additional studies using inductive (exploration) and deductive
31 (hypotheses-driven) approaches will be useful in determining the relationships
32 between VMI and neural structure.
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3 VMI performance is dependent on fine motor skills. And, fine motor skills have been
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5 shown to be a facilitator of visuo-motor function even though the causality of this
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7 mediation is not known ⁴⁶. The present study revealed positive correlations between
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9 better fine motor skills and larger volumes of the precentral gyrus, the cerebellum and
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11 the brainstem - motor areas of the brain that have been reported to be involved in
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13 fine motor skills ⁵⁰. The precentral gyrus, which is located in the frontal lobe, is the
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15 origin of the corticospinal tracts known to affect motor functions. A smaller precentral
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17 gyrus could, therefore, be expected to be correlated with reduced motor performance
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19 and also to diminished VMI performance, in line with our findings, since fine motor
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21 skills have been shown to be a mediator of visuo-motor function, even though the
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23 cause of this mediation is not known ⁴⁶. Both the cerebellum and the brain stem are
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25 important for fine motor skills and VMI, as well as for other tasks that rely on the
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27 motor system ⁴⁷, and our results support their important role in this cross-modal
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29 function. In addition, the cerebellum has long been known to be involved in
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31 movement modulation, balance and coordination, and there is now evidence that it is
32
33 also important for a number of cognitive functions, including visuospatial attention ⁵¹.
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35 Finally, cerebellar growth has been shown to relate to visual perception at school age
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37 in children born very preterm ⁵² and specific sub-regional volumes of the cerebellum
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39 have been shown to be related to VMI and influenced by other perinatal factors, such
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41 as pain and infections⁵². Taken together, the literature suggests that neurocorrelates
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43 for fine motor skills are important for VMI performance as well, whether the
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45 neurocorrelates are contributing to VMI performance directly, or indirectly, through
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47 fine motor skills. The current findings suggest that the brain growth of the precentral
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49 gyrus, cerebellum and brainstem have already altered during the neonatal period and
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51 that this affects functions such as VMI and fine motor skills.
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3 We were surprised to find a negative correlation between cortical grey matter volume
4 and fine motor skills in our cohort, despite the fact that Keunen et al reported a
5 similar finding. Those authors also reported an inverse relationship between cortical
6 grey matter volume and fine motor function when children who were born preterm
7 reached 2.5 years²⁰. Measuring the cortical grey volume depends on the
8 segmentation methods used to separate grey matter from the cerebellum which could
9 make the classifying cortical grey matter volume imprecise. It is also possible that
10 atypical patterns of brain development play a role in the grey matter volume and fine
11 motor skills relationship, in the preterm brain¹⁶.

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23 A strength of this study is its population-based prospective cohort study design. The
24 study focused on children born EPT without major brain lesions, which meant that our
25 cohort was relatively healthy. This was reflected in their average range performances
26 on both the VMI and the fine motor skills tests, with a mean of only -0.5 SD below the
27 norms, which is higher than previously reported in preterm populations. This study
28 also has several limitations. We had to exclude many children from the morphometric
29 analyses, due to the strict criteria for data quality, and this was a reflection of the
30 well-known difficulties in processing neonatal MRI images in children born EPT. This
31 left us with a relatively small sample size, although the children with morphometric
32 data were largely representative of the whole cohort. Visual-motor integration was
33 assessed with the main Beerys VMI test, but did not include the supplementary tests
34 of visual perception and motor coordination which could have enabled us to
35 distinguish between visual perception and fine motor function with regard to the VMI
36 function. Finally, we were not able to include a control group of children born at term.

37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 *Conclusion*

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55 In summary, this study found positive correlations between VMI performance, fine
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3 motor skills and brain volumes at term-equivalent age in regions that were already
4 known to be involved in these functions. To our knowledge, this is the first study to
5 examine the relationship between neonatal brain volumes and VMI and fine motor
6 skills at the age of 6.5 years in a population-based cohort of children born EPT.
7
8 Further studies including larger sample sizes are needed to confirm our results, to
9 explore the relationships between the underlying visual and motor modalities and
10 VMI in greater depth, and to examine the potential use of early regional brain
11 volumes as imaging biomarkers related to VMI and fine motor skills. Since it has
12 been reported that early interventions can improve VMI in general school populations
13 ⁵³ as well as in children born preterm ⁵⁴, a possibility of early identification of children
14 at risk could diminish the impact of preterm birth on these functions.
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27 **Ethical approval:** All procedures performed in studies involving human participants
28 were in accordance with the ethical standards of the institutional and/or national
29 research committee and with the 1964 Helsinki declaration and its later amendments
30 or comparable ethical standards.
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37 **Informed consent:** Informed consent was obtained from the parents of all individual
38 participants included in the study.
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42 **Author's contributions:**

43
44 J Bolk designed the study, collected data, performed analyses, interpreted the data,
45 drafted and revised the manuscript and approved the final version.
46
47

48 N Padilla designed the study, collected data, performed analyses, interpreted the
49 data, revised the manuscript and approved the final version.
50
51

52 L Broström collected data, interpreted data, revised the manuscript and approved the
53 final version.
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3 L Forsman collected data, interpreted data, revised the manuscript and approved the
4
5 final version.

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7 K Hellgren collected data, interpreted data, revised the manuscript and approved the
8
9 final version.

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11 U Åden designed the study, collected data, interpreted the data, revised the
12
13 manuscript and approved the final version
14

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21 possible.

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23
24 We want to thank our research nurse Lena Swartling-Schlinzig and our psychologist
25
26 Eva Eklöf, the NeoBIG group and the EXPRESS group.
27

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29
30 **Abbreviations:** *Cerebral palsy (CP), Sum of grey and white matter excluding*
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32 *cerebrospinal fluid (CPAR), Extremely Preterm Born (EPT), Gestational age (GA),*
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34 *Magnetic Resonance Imaging (MRI), Movement Assessment Battery for Children-2*
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36 *(M-ABC), Standard Deviation (SD), Visual-motor integration (VMI)*
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40 **Data sharing statement:** Any requests for data sharing should be addressed to
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42 author U.Å.
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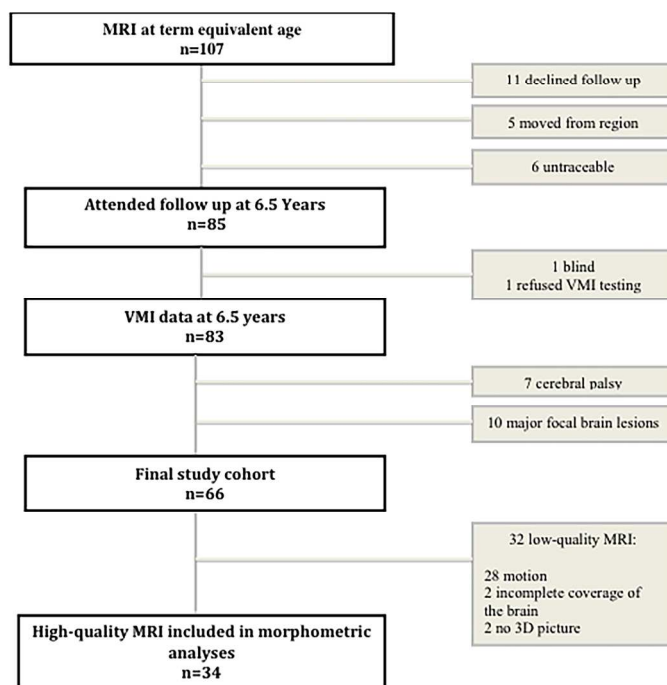


Figure 1. Study population

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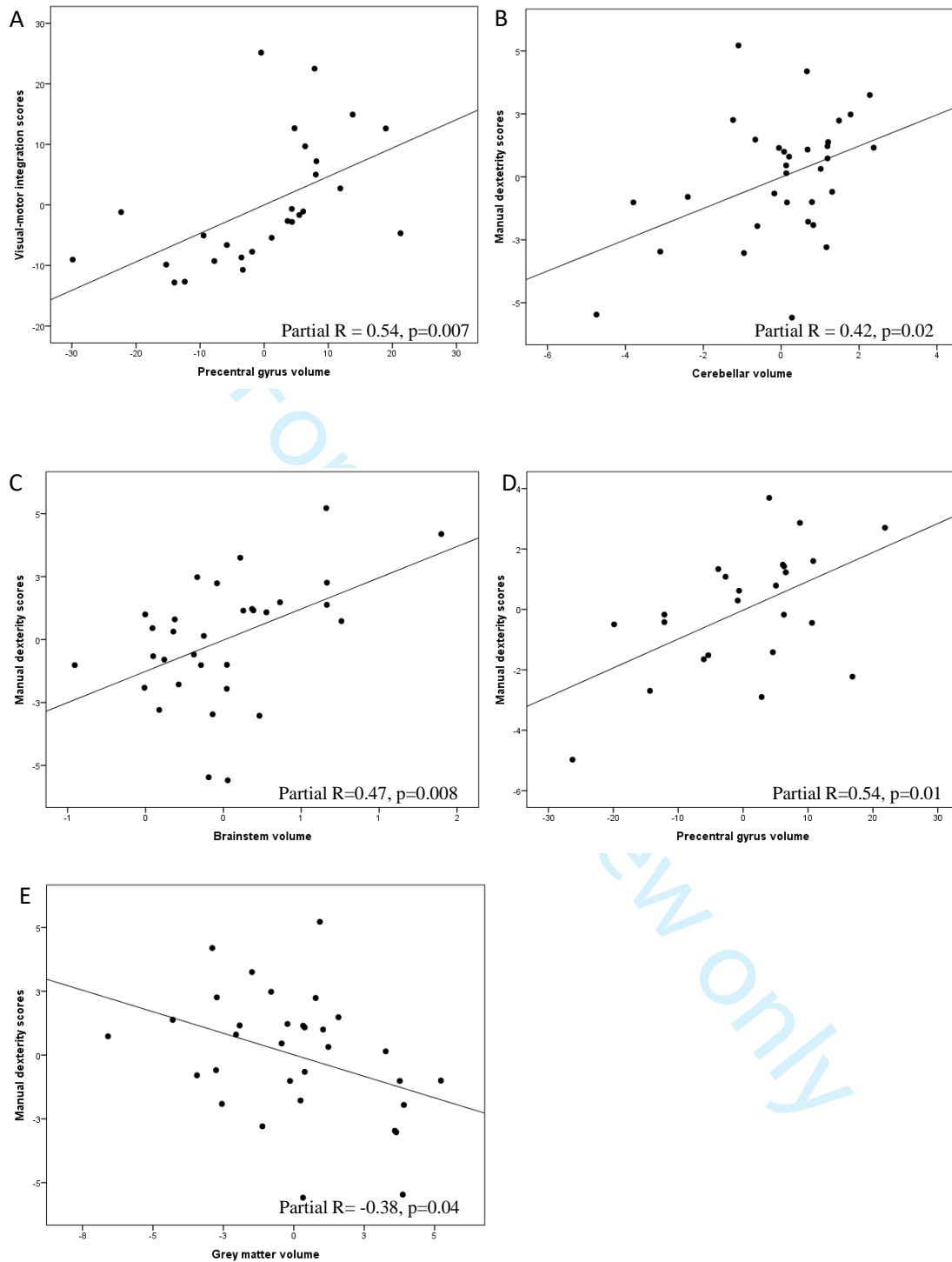


Figure 2. Illustrations of partial correlations between neonatal brain volumes, visual-motor integration and fine motor skills (assessed by manual dexterity scores on the Movement Assessment Battery for Children-2) at 6.5 years of age, using plots of residuals. Analyses are adjusted for total cerebral parenchyma (grey matter plus white matter) and sex. (A) Correlations between the volume of the precentral gyrus and visual-motor integration scores. (B-E) Correlations between the volumes of the cerebellum, brainstem, precentral gyrus, grey matter and fine motor skills.

Table 1. Characteristics of the 66 children born at gestational age below 27 weeks and without major brain lesions or cerebral palsy (n = 66)

Gestational age at birth, weeks, median (range)	25.6 (23.4-26.6)
Birth weight, grams, mean (SD)	839 (152)
Gender, girls/boys	29/37
Small for gestational age, n (%)	4 (6)
Prenatal steroids, n (%)	60 (91)
Premature Rupture of the Membranes, n (%)	19 (29)
Cesarean section, n (%)	32 (48)
Sepsis, n (%)	51 (77)
Days of mechanical ventilation, median (range)	7 (0-55)
Postnatal steroids, n (%)	11 (17)
Bronchopulmonary dysplasia, oxygen at 36 weeks, n (%)	26 (39)
Necrotizing Enterocolitis, n (%)	6 (9)
Patent Ductus Arteriosus, ligation, n (%)	20 (30)
Laser treatment for Retinopathy of Prematurity, n (%)	8 (12)
Intraventricular hemorrhage grade I-II, n (%)	23 (35)

SD = Standard Deviation, n = number. Sepsis was defined as positive blood culture or clinical picture of sepsis in association with elevated C-reactive protein or leukocyte count. Data on small for gestational age was missing for four children.

Supplementary Table 1. Characteristics of the children born at gestational age <27 weeks with or without high quality MRI

	High quality MRI n=34	Low quality MRI n=32	<i>p</i>
Gestational age at birth, weeks, median (range)	25.85 (23.4-26.6)	25.45 (23.4-26.6)	0.16
Birth weight, grams, mean (SD)	857 (154)	820 (47)	0.33
Gender, girls/boys, n	15/19	14/18	1.00
Small for gestational age, n	1	3	0.35
Prenatal steroids, n	32	28	0.42
Premature rupture of the membranes, n	10	9	1.00
Cesarean section, n	16	16	1.00
Sepsis, n	24	27	0.24
Days of mechanical ventilation, median (range)	3 (0-37)	11 (0-55)	0.04
Postnatal steroids, n	4	7	0.33
Bronchopulmonary Dysplasia, oxygen at 36 weeks, n	12	14	0.62
Necrotizing enterocolitis, n	1	5	0.10
Patent ductus arteriosus, ligation, n	9	11	0.60
Laser treatment for retinopathy of prematurity, n	2	6	0.14
Intraventricular hemorrhage grade I-II, n	10	13	0.44
Mild white matter abnormality, n	18	12	0.09
Gestational age at MRI, weeks, median (range)	40.79 (39.14-45.28)	40.28 (39.14-43.28)	0.08
Age at 6.5 year assessment, months, median (range)	77.20 (75.29-80.18)	77.23 (76.03-86.33)	0.59
VMI standard score, mean (SD)	94 (10)	91 (9)	0.20
M-ABC-2 manual dexterity score, mean (SD)	8 (2)	7 (3)	0.68

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3 All children were without cerebral palsy, focal brain lesions or severe white matter
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5 abnormalities. SD = Standard deviation, MRI = Magnetic Resonance Imaging, VMI=Visual-
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7 motor integration, M-ABC-2=Movement Assessment Battery for Children-2
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Supplementary Table 2. Characteristics of the children born at gestational age <27 weeks with and without atlas segmentation data.

	Atlas segmentation data n=26	No atlas segmentation data n=40	<i>p</i>
Gestational age at birth, weeks, median (range)	26.85 (23.4-26.6)	25.50 (23.4-26.6)	0.28
Birth weight, grams, mean (SD)	874 (153)	817 (146)	0.13
Gender, girls/boys	13/13	16	0.46
Small for gestational age, n	0	4	0.15
Prenatal steroids, n	25/26	35	0.39
Premature rupture of the membranes, n	7	12	1.00
Cesarean Section, n	10	22	0.22
Sepsis, n	17	34	0.08
Days of mechanical ventilation, median (range)	3 (0-36)	10 (0-55)	0.04
Postnatal steroids, n	3	8	0.51
Bronchopulmonary Dysplasia, oxygen at 36 weeks, n	10	16	1.00
Necrotizing enterocolitis, n	0	6	0.07
Patent ductus arteriosus, ligation, n	7	13	0.79
Laser treatment for retinopathy of prematurity, n	1	7	0.13
Intraventricular hemorrhage grade I-II, n	7	16	0.30
Mild white matter abnormality, n	16	14	0.09
Gestational age at MRI, weeks, median (range)	40.93 (39.71-43.28)	40.36 (39.14-45.28)	0.18
Age at 6.5 year assessment, months, median (range)	77.16 (75.29-80.20)	77.23 (76.03-86.33)	0.21
VMI standard score, mean (SD)	91.69 (14.14)	89.82 (11.71)	0.87

M-ABC-2 manual dexterity score, mean (SD)	7 (2)	8 (3)	0.38
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All children were without cerebral palsy, focal brain lesions or severe white matter abnormalities.

SD = Standard deviation, MRI = Magnetic Resonance Imaging, VMI=Visual-motor integration, M-ABC-2=Movement Assessment Battery for Children-2

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Supplementary Table 3. Correlations between brain volumes at term equivalent age, visual-motor integration and fine motor skills scores a 6.5 years in children born at GA <27 weeks.

Brain region	Visual-motor integration		Fine motor skills	
	Correlation coefficient (partial r)	p	Correlation coefficient (partial r)	p
Grey matter	0.05	0.77	-0.38	0.04
White matter	-0.33	0.07	0.11	0.57
Deep grey matter	0.02	0.93	0.05	0.79
Cerebellum	0.24	0.19	0.42	0.02
Brain stem	0.08	0.66	0.47	0.008
Frontal lobe	-0.11	0.61	-0.19	0.40
Temporal lobe	-0.10	0.63	-0.12	0.61
Parietal lobe	-0.33	0.12	-0.22	0.32
Occipital lobe	0.18	0.40	0.26	0.24
Central Region	0.35	0.09	0.30	0.17
Networks				
Visual network				
Superior occipital gyrus	0.23	0.28	0.39	0.07
Middle occipital gyrus	0.12	0.59	0.06	0.78
Inferior occipital gyrus	-0.26	0.22	-0.21	0.35
Calcarine cortex	-0.24	0.27	-0.01	0.97
Cuneus	0.27	0.20	0.20	0.37
Lingual gyrus	-0.13	0.54	-0.01	0.67
Motor network				
Precentral gyrus	0.54	0.007	0.54	0.01
Frontal medial	0.005	0.99	-0.05	0.83
Supplementary motor area	-0.03	0.89	-0.19	0.40
Sensory network				
Postcentral gyrus	0.07	0.75	0.17	0.45
Salience network				
Insula	-0.001	0.99	-0.08	0.73
Anterior cingulate gyrus	0.09	0.67	0.10	0.65
Thalamus	-0.04	0.87	0.11	0.62
Amygdala	-0.16	0.45	-0.23	0.31
Default mode network				
Precuneus	-0.26	0.22	-0.05	0.84
Angular gyrus	0.26	0.21	-0.17	0.45
Hippocampus	-0.08	0.72	-0.11	0.63
Subcortical regions				
Subcortical grey matter, total	-0.10	0.63	-0.04	0.86
Pallidum	0.01	0.99	0.07	0.76

Caudate	-0.04	0.85	-0.09	0.70
Putamen	-0.26	0.23	0.06	0.79

All children are without cerebral palsy or major brain lesions. Results from Pearson's partial correlation, adjusted for total cerebral parenchyma (total cortical grey and white matter) and sex. Central region = precentral and postcentral gyri, rolandic operculum bilaterally.

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BMJ Open

Visual-motor integration and fine motor skills at 6.5 years of age and associations with neonatal brain volumes in children born extremely preterm in Sweden: population-based cohort study

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Neurology
Keywords:	outcome, extremely preterm born child, brain development, school-age, visual-motor integration, fine motor skills

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3 **Visual-motor integration and fine motor skills at 6.5 years of age and**
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10 Jenny Bolk, M.D.^{1,2}, Nelly Padilla M.D, PhD¹, Lea Forsman, PhD¹, Lina Broström,
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48 **Abstract**

49 *Objectives*

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52 This exploratory study aimed to investigate associations between neonatal brain
53 volumes and visual-motor integration (VMI) and fine motor skills in children born EPT
54 when they reached 6.5 years of age.
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Setting

Prospective population-based cohort study in Stockholm, Sweden, during three years.

Participants

All children born before gestational age 27 weeks 2004-2007 in Stockholm, without major morbidities and impairments, and who underwent magnetic resonance imaging at term-equivalent age.

Main outcome measures

Brain volumes were calculated using morphometric analyses in regions known to be involved in VMI and fine motor functions. VMI was assessed with The Beery-Buktenica Developmental Test of Visual-Motor Integration - Sixth Edition and fine motor skills were assessed with the manual dexterity subtest from the Movement Assessment Battery for Children-Second Edition, at 6.5 years. Associations between the brain volumes and VMI and fine motor skills were evaluated using partial correlation, adjusted for total cerebral parenchyma and sex.

Results

Out of 107 children born at gestational age <27 weeks, 83 were assessed at 6.5 years and 66/83 were without major brain lesions or cerebral palsy and included in the analyses. A representative subsample underwent morphometric analyses: automatic segmentation (n=34) and atlas-based segmentation (n=26). The precentral gyrus was associated with both VMI ($r=0.54$, $p=0.007$) and fine motor skills ($r=0.54$, $p=0.01$). Associations were also seen between fine motor skills and the volume of the cerebellum ($r=0.42$, $p=0.02$), brainstem ($r=0.47$, $p=0.008$) and grey matter ($r=-0.38$, $p=0.04$).

Conclusions

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3 Neonatal brain volumes in areas known to be involved in VMI and fine motor skills
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5 were associated with scores for these two functions when children born EPT without
6
7 major brain lesions or cerebral palsy were evaluated at 6.5 years of age. Establishing
8
9 clear associations between early brain volume alterations and later VMI and/or fine
10
11 motor skills could make early interventions possible.
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14 **Strengths and limitations of this study**

- 17 • This was a robust population-based cohort study design that used advanced
18 magnetic resonance imaging techniques and established assessment tools
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- 21 • It studied visual-motor integration and fine motor skills in extremely preterm
22 born children at 6.5 years, which is an important age for Swedish school
23 children
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- 26 • Although we had to exclude numerous children from the morphometric
27 analyses, due to strict data quality criteria, the sample was representative of
28 the cohort
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- 31 • We were unable to include a control group of children born at term in the
32 analyses
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17 publication.
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47 **Introduction**

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50 Visual-motor function is an important cross-modal ability that involves the integration
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52 of visual function and perception, eye-hand coordination, fine motor skills and visual-
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54 motor integration (VMI) ¹. Studies have shown that VMI can predict a child's future
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3 hand-writing skills²⁻⁴ and academic performance in reading, writing and mathematics
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5⁵. Evaluating VMI performance is therefore an important component of the test
6
7 batteries that are used to detect children who risk school problems. Fine motor skills
8
9 are a fundamental component of hand and visual-motor function, which also
10
11 contributes to school performance⁶. Several reports have shown that children born
12
13 preterm have poor VMI and motor function^{7 8-10} and it is well known that this group of
14
15 children risk poor school performance and learning disabilities¹¹⁻¹³.

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18 Although problems with VMI can stem from any of the underlying, contributing
19
20 abilities listed above, when VMI and motor abilities have been investigated together,
21
22 and perceptual and general cognitive abilities have been held constant, children with
23
24 lower general motor scores are seen to have lower VMI scores¹⁴. Children born very
25
26 low birth weight show a similar pattern¹⁵: VMI showing stronger relationships with
27
28 motor ability than with visual perception, suggesting that motor skills and manual fine
29
30 motor skills in particular, are crucial components underlying VMI. On the other hand,
31
32 visual perceptual deficits in children born EPT are well documented⁷ and their role in
33
34 VMI should not be underestimated even though their contribution to VMI in children
35
36 born EPT was not investigated in the present study. Therefore, a less-defined
37
38 exploration of brain areas known to be associated with VMI is a useful approach,
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40 especially when investigating the neural associations of a multi-modal ability, in
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42 groups with potentially atypical brain development trajectories¹⁶.

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47 It is largely unknown how the developmental alterations of the brain affect VMI and
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49 fine motor skills in children born preterm. However, we have previously reported that
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51 neonatal brain volumes are affected in preterm infants¹⁷, and other researchers have
52
53 shown that these alterations in preterm brain volumes persist until at least early
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55 childhood¹⁸. Volumetric alterations in the brain have also been associated with
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3 neurodevelopmental outcomes in preterm born children^{19 20}. However, the
4
5 relationship between volume alterations in the brains of children born extremely
6
7 (EPT), at less than 27 weeks of gestation, and VMI and fine motor skills at school
8
9 age remains largely unexplored.

10
11 It has been reported that several networks in the brain are involved in the mediation
12
13 of VMI and fine motor skills - the visual, salience, sensory motor and default mode
14
15 networks²¹. Previous studies in adolescents born preterm have indicated that
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17 volumes of the cerebellum and thalamus²², superior temporal gyrus, insula, medial
18
19 occipital lobe and temporal lobe²³ are associated to VMI scores. Also, a study
20
21 looking at brain growth in preterm children reported that growth of the caudate and
22
23 globus pallidus could predict VMI scores²⁴. Based on these previous reports, we
24
25 hypothesized that early brain volume alterations in these regions and networks in the
26
27 brain would be related to later VMI and fine motor skills in Children born extremely
28
29 preterm. We used an exploratory approach to investigate these possible associations,
30
31 using two separate analyses to measure the brain volumes at term-equivalent age :
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33 atlas-based segmentation and automatic segmentation, and carried out a clinical
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35 evaluation of VMI and fine motor skills at the age of 6.5 years.
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43 **Methods**

44 ***Study population***

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46 The study population was a sub-cohort of the Extremely Preterm Infants in Sweden
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48 Study (EXPRESS) cohort. EXPRESS was a prospective national population-based
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50 cohort study which invited all children born in Sweden at a gestational age (GA) of
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52 less than 27 weeks over a three-year period to take part in clinical follow ups at 2.5
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54 and 6.5 years of age^{25 26}. The present study included 107 children born in Stockholm
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3 between January 1 2004 and March 31 2007, without chromosomal aberrations,
4 congenital malformations or infections, who had undergone magnetic resonance
5 imaging (MRI) of the brain at term equivalent age.
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9 Gestational age was assessed by maternal ultrasound at around a GA of 18 weeks
10 and perinatal and neonatal data were prospectively collected from the children's
11 medical records. Cranial ultrasound was performed on a regular basis during the
12 neonatal period up to a GA of 40 weeks, according to our clinical routine. Children
13 were excluded from the analyses in the present study if they had major brain lesions
14 defined as intraventricular hemorrhage, periventricular leukomalacia, severe white
15 matter score according to Inder ²⁷ or hydrocephalus, or cerebral palsy (CP) as
16 defined by the Surveillance of Cerebral Palsy in Europe Working Group ²⁸. All
17 children had been screened for retinopathy of prematurity and evidence-based
18 treatment had been administered ²⁹.
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31 The study was approved by the local ethics committees in Stockholm and Lund
32 (Regionala etikprövningsnämnden in Stockholm, dnr 04-889/2, 2006/1217-32 and
33 2010/850-31/1; Regionala etikprövningsnämnden in Lund, dnr 42/2004, dnr 2009/9
34 and dnr 2016/104) and the parents of all the children gave their written, informed
35 consent before the study.
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41 42 **Assessment at 6.5 years of age**

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45 Visual-motor integration was assessed using the Beery-Buktenica Developmental
46 Test of Visual-Motor Integration - sixth edition ³⁰. This test consists of 30 geometrical
47 shapes that the child is asked to copy with a pen and paper and it is terminated when
48 three figures in a row have been incorrectly copied. The drawings are examined and
49 acceptable approximations of the model drawings are each given one point. The raw
50 score is the total number of correct drawings and this is then transformed to an age-
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3 corrected standard score. Standard scores were used in the analyses in this study.

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5 The normative mean score is 100 with a standard deviation (SD) of 15.

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7 Fine motor skills were assessed with the manual dexterity subtest of the Movement
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9 Assessment Battery for Children – Second edition (M-ABC-2) which measures
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11 unimanual speed, bimanual coordination and unimanual spatial accuracy³¹. Age-
12
13 adjusted standard scores were used for the analyses. The reference mean score is
14
15 10 with a standard deviation of 3, and scores below 7 indicate definitive or borderline
16
17 motor problems.

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19 Binocular visual acuity was measured with habitual correction at three meters with
20
21 the Lea Hyvärinen chart³². Visual impairment was defined as a visual acuity of less
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23 than 0.33 in the better eye.
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26 27 ***MRI data acquisition and processing***

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29 All the children were scanned using a Philips Intera 1.5 Tesla MRI system (Philips
30
31 International, Amsterdam, The Netherlands) at term equivalent age.. The child was
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33 fed before the scanning procedure and given a low dose of chloralhydrate (30 mg/kg)
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35 orally or rectally, as previously described³³. A sagittal T1-weighted turbo spin echo
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37 sequence, an axial inversion recovery sequence and an axial T2-weighted sequence
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39 were run. The three-dimensional T1-weighted images were acquired with an echo
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41 time of 4.6 msec, a repetition time of 40 msec, a flip angle of 30°, a voxel size of 0.7
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43 × 0.7 × 0.1 mm and a field of view of 180mm. The MRI protocol has previously been
44
45 reported³³. Quality assurance was considered important in order to obtain accurate
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47 data, even though this meant that we were left with a relatively small sample size.
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49 The imaging data was checked for quality, based on a visual inspection of the raw
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51 data sets, and the reasons for low imaging quality are presented in **Figure 1**. MRI
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53 data went into two separate analyses, atlas based segmentation and automatic
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3 segmentation; atlas-based segmentation to conduct the regional segmentation of
4 specific regions ³⁴ and automatic segmentation to extract the mean volumes of the
5 grey matter white matter, cerebrospinal fluid, basal ganglia, brainstem and
6 cerebellum ³⁵.
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11 ***Atlas based segmentation***

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14 The whole brain of the included infants was divided into 90 anatomical regions, by
15 using the automated anatomical labelling neonatal atlas ³⁴, as previously described
16 ³⁶. Briefly, the intensity image that generated the neonatal atlas was registered to the
17 T1-weighted image of each infant, then the generated deformation field was used to
18 transform the label map with 90 regions from the atlas space to the subject space
19 (Supplementary Figure 1). A visual inspection was performed for each subject and
20 each step. The volume of each region was determined by using a proper script
21 written in MATLAB selecting the region of interest via its voxel value.
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31 We selected brain regions that had been previously described as being in the
32 networks that mediate VMI and fine motor skills, namely the visual, salience, sensory
33 motor and default mode networks ²²⁻²⁴. We also considered the subcortical regions:
34 pallidum, putamen, caudate and thalamus. The volume of each brain region was
35 determined by adding together the volumes of their components.
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43 ***Automatic segmentation***

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45 We first performed automatic segmentation of brain tissues (T1-weighted images)
46 using SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm>), running on MATLAB version
47 7.5 (MathWorks, Natick, Massachusetts, USA). This process focused on specific
48 neonatal priors, including grey matter, white matter, cerebrospinal fluid, deep grey
49 matter, the cerebellum and brainstem, which have previously been described in detail
50 ^{17 35}. We used the tissue class images created during segmentation to generate a
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3 custom template to improve coregistration using Diffeomorphic Anatomical
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5 Registration Through an Exponential Lie algebra algorithm (DARTEL).³⁷ After this
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7 step the images were modulated via SPM 8 software to improve the inter-subject
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9 registration.. The Easy Volume Toolbox³⁸ was used to extract the global brain tissue
10
11 volumes from the segmented, normalized and modulated images of each child.
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14 **Statistical analyses**

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16 The analyses were carried out with SPSS for Windows, version 22.0 (SPSS Inc,
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18 Chicago, Illinois, USA) and the data were checked for normality, homogeneity and
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20 outliers. In order to compare the groups, we used the Student's t-test and Mann
21
22 Whitney U test for continuous variables and the chi-square test or Fisher's exact test
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24 for categorical data, as appropriate. The associations between brain volumes, VMI
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26 scores and fine motor skills scores were explored using partial correlation. Total
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28 cerebral parenchyma (CPAR) – the sum of the grey matter and white matter,
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30 excluding cerebrospinal fluid - was used as a covariate to control for generalized
31
32 scaling effects. Because sex, GA at birth and the GA at the time of the scan have
33
34 previously been shown to influence brain volume size in preterm children^{39 40} we
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36 performed the analyses with different covariate pairs. First we used CPAR and GA at
37
38 birth, then we used CPAR and the GA at scan and finally we used CPAR and sex.
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40 GA at birth and GA at scan did not influence the results, but sex did, so CPAR and
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42 sex were chosen as the covariates in the final model. There was one multivariate
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44 outlier which was identified by the Mahalanobis distance when we investigated the
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46 atlas segmentation data in relation to the fine motor skills scores, and this child was
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48 excluded from those analyses. Bonferroni's correction for multiple comparisons was
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50 not applied because of the exploratory nature of the study and the reduced sample
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52 size examined⁴¹⁻⁴³. The level of significance was set at a two-sided p-value of <0.05.
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Results

Study population

A summary of the study population is presented in **Figure 1** and their perinatal characteristics are presented in **Table 1**.

Table 1. Characteristics of the 66 children born at gestational age below 27 weeks and without major brain lesions or cerebral palsy (n = 66)

Gestational age at birth, weeks, median (range)	25.6 (23.4-26.6)
Birth weight, grams, mean (SD)	839 (152)
Gender, girls/boys	29/37
Small for gestational age, n (%)	4 (6)
Prenatal steroids, n (%)	60 (91)
Premature Rupture of the Membranes, n (%)	19 (29)
Cesarean section, n (%)	32 (48)
Sepsis, n (%)	51 (77)
Days of mechanical ventilation, median (range)	7 (0-55)
Postnatal steroids, n (%)	11 (17)
Bronchopulmonary dysplasia, oxygen at 36 weeks, n (%)	26 (39)
Necrotizing Enterocolitis, n (%)	6 (9)
Patent Ductus Arteriosus, ligation, n (%)	20 (30)
Laser treatment for Retinopathy of Prematurity, n (%)	8 (12)
Intraventricular hemorrhage grade I-II, n (%)	23 (35)

SD = Standard Deviation, n = number. Sepsis was defined as positive blood culture or clinical picture of sepsis in association with elevated C-reactive protein or leukocyte count. Data on small for gestational age was missing for four children.

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6 At the time of the scan, the median (range) GA in the 66 children without major brain
7 lesions or CP was 40.8 (39.1-45.3) weeks and for the assessment of VMI and fine
8 motor skills it was 6 years 5 months (6 years 3 months - 7 years 2 months).

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12 The subsample of 34 children with high-quality MRI scans was representative of the
13 whole cohort with regard to their perinatal and neonatal characteristics, findings on
14 structural MRI, gestational age at MRI, age at assessment at 6.5 years and mean
15 VMI and fine motor score (**Supplementary Table 1**). During the atlas-based
16 segmentation process, 8 subjects had co-registration failure, leaving 26 children in
17 the final sample. These 26 children were also representative of the cohort of 66
18 children with regard to the above characteristics, except for days on mechanical
19 ventilation, which was a median (range) of 3 (0-36) days for the sub-sample versus
20 10 (0-55) days for the other children ($p=0.04$) (**Supplementary Table 2**).

31 32 33 **Assessment at 6.5 years of age**

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36 The mean (SD) VMI standard score for the 66 children without major brain lesions or
37 CP was 93 (10), 7 points (0.5 SD) below the norm. The mean (SD) VMI scores for
38 the 29 girls was higher than for the 37 boys: mean (SD) at 96 (10) versus 90 (8),
39 respectively ($p=0.02$).

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41
42 The mean (SD) fine motor skills score was 8 (3), which was 2 points (0.5 SD) below
43 the norm, and there were no significant sex differences as the girls scored 8 (3) and
44 the boys 7 (3) ($p=0.16$).

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47 None of the children included in the study had a visual impairment.

48 49 50 **Brain volumes and associations with VMI and fine motor skills**

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53 We identified a number of regions that demonstrated significant associations

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3 between brain volumes, VMI and fine motor skills scores. VMI performance showed a
4 positive correlation with the volume of the precentral gyrus (partial $r=0.54$, $p=0.007$),
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6 whereas the fine motor skills scores showed a positive correlation with the volumes
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8 of the precentral gyrus (partial $r = 0.54$, $p=0.01$), the cerebellum (partial $r = 0.42$,
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10 $p=0.02$) and the brainstem (partial $r = 0.47$ $p=0.008$) and a negative correlation with
11
12 cortical grey matter volume (partial $r = -0.38$, $p=0.04$) (**Figure 2**). All the correlation
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14 analyses can be found in **Supplementary Table 3**.
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17 18 **Discussion**

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20 In this exploratory study, the associations between brain volumes at term equivalent
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22 age and VMI and fine motor skills at 6.5 years in children born EPT without major
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24 brain lesions or CP were explored in regions of the brain previously reported to be
25
26 involved in those functions. The volume of the precentral gyrus showed a positive
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28 correlation with both VMI and fine motor skills, and the volumes of the cerebellum
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30 and the brainstem correlated positively to fine motor skills. Total cortical grey matter
31
32 volume showed a negative correlation with fine motor skills.
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36 The group scores for the children included in this study were below the test norms on
37
38 both VMI and fine motor skills, which was in line with previous studies where children
39
40 born preterm have consistently shown poorer VMI performance and fine motor skills
41
42 compared to children born at term^{7 44}. However, the lower group performance is still
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44 considered to be within low average range. Within this relatively well-functioning
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46 group of children born EPT, we found a small, but statistically significant, difference
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48 between the sexes with regards to VMI performance, with girls outperforming boys.
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50 Sex differences in VMI performance have consistently been reported in children born
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52 preterm⁷ and MRI studies of children born preterm have revealed differences
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54 between the sexes in brain volumes and the microstructure of the brain^{39 45 46},
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3 indicating altered early development of the brain in boys born preterm. This indicates
4 that the brain of preterm born boys develops in an altered way compared to preterm
5 born girls, affecting both the structure and the function of the brain.
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10 Cerebellar underdevelopment, with reductions in cerebellar volume, and sustained
11 white matter injuries in children born preterm, have been suggested as possible
12 mechanisms for poor visuo-motor function^{47 9 23}, although many neural networks
13 comprised of other neural structures have also been proposed to be involved in VMI
14 including the visual, motor, sensory, salience and default mode networks, the
15 subcortical regions and the brain stem^{21 48}. Even though this study is the first, to our
16 knowledge, to explore the associations between brain volumes at term equivalent
17 age and VMI at 6.5 years in a cohort of children born EPT, there have been previous
18 reports of associations between brain volumes and VMI performance in more mature
19 preterm children. In these reports, positive correlations were seen between the
20 growth rate of the caudate and the thalamus during the neonatal period and VMI
21 scores at 4 years of age²⁴, and between thalamic and cerebellar white matter
22 volumes and VMI scores at 15 years of age²². We did not find these associations in
23 our cohort and this finding was in line with a previous study that evaluated 8-year-old
24 children born preterm⁴⁹. One explanation for these different results could be
25 individual childhood growth trajectories and different gestational ages in the various
26 study cohorts. Additional studies using inductive (exploration) and deductive
27 (hypotheses-driven) approaches will be useful in determining the relationships
28 between VMI and neural structure.
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51 VMI performance is dependent on fine motor skills. And, fine motor skills have been
52 shown to be a facilitator of visuo-motor function even though the causality of this
53 mediation is not known⁴⁷. The present study revealed positive correlations between
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3 better fine motor skills and larger volumes of the precentral gyrus, the cerebellum and
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5 the brainstem - motor areas of the brain that have been reported to be involved in
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7 fine motor skills⁵⁰. The precentral gyrus, which is located in the frontal lobe, is the
8
9 origin of the corticospinal tracts known to affect motor functions. A smaller precentral
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11 gyrus could, therefore, be expected to be correlated with reduced motor performance
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13 and also to diminished VMI performance, in line with our findings, since fine motor
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15 skills have been shown to be a mediator of visuo-motor function, even though the
16
17 cause of this mediation is not known⁴⁷. Both the cerebellum and the brain stem are
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19 important for fine motor skills and VMI, as well as for other tasks that rely on the
20
21 motor system⁴⁸, and our results support their important role in this cross-modal
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23 function. In addition, the cerebellum has long been known to be involved in
24
25 movement modulation, balance and coordination, and there is now evidence that it is
26
27 also important for a number of cognitive functions, including visuospatial attention⁵¹.
28
29 Finally, cerebellar growth has been shown to relate to visual perception at school age
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31 in children born very preterm⁵² and specific sub-regional volumes of the cerebellum
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33 have been shown to be related to VMI and influenced by other perinatal factors, such
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35 as pain and infections⁵². Taken together, the literature suggests that neurocorrelates
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37 for fine motor skills are important for VMI performance as well, whether the
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39 neurocorrelates are contributing to VMI performance directly, or indirectly, through
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41 fine motor skills. The current findings suggest that the brain growth of the precentral
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43 gyrus, cerebellum and brainstem have already altered during the neonatal period and
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45 that this affects functions such as VMI and fine motor skills.

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51 We were surprised to find a negative correlation between cortical grey matter volume
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53 and fine motor skills in our cohort, despite the fact that Keunen et al reported a
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55 similar finding. Those authors also reported an inverse relationship between cortical
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3 grey matter volume and fine motor function when children who were born preterm
4 reached 2.5 years ²⁰. Measuring the cortical grey volume depends on the
5
6 segmentation methods used to separate grey matter from the cerebellum which could
7
8 make the classifying cortical grey matter volume imprecise. It is also possible that
9
10 atypical patterns of brain development play a role in the grey matter volume and fine
11
12 motor skills relationship, in the preterm brain ¹⁶.
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16
17 A strength of this study is its population-based prospective cohort study design. The
18
19 study focused on children born EPT without major brain lesions, which meant that our
20
21 cohort was relatively healthy. This was reflected in their average range performances
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23 on both the VMI and the fine motor skills tests, with a mean of only -0.5 SD below the
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25 norms, which is higher than previously reported in preterm populations. This study
26
27 also has several limitations. We had to exclude many children from the morphometric
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29 analyses, due to the strict criteria for data quality, and this was a reflection of the
30
31 well-known difficulties in processing neonatal MRI images in children born EPT. This
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33 left us with a relatively small sample size, although the children with morphometric
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35 data were largely representative of the whole cohort. This was due to rigorous entry
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37 and data quality criteria, as well as implicit methodological difficulties related to the
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39 scanning of preterm infants. Scanning preterm neonates is considered a challenging
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41 task due to their immature physiology and anatomy. Patient motion may occur more
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43 often thus patient preparation and image protocols should be modified and be
44
45 dedicated for neonates. To minimize this limitation the development of novel pulse
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47 sequences to increase the speed of image acquisition, and MRI coils tailored to the
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49 head size of the subject, would have the potential to further increase success ⁵³.
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53
54 Segmentation of cerebral tissues at term-equivalent age in children who were born
55
56 extremely preterm is challenging due to the characteristics of the developing preterm
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2
3 brain. The segmentation can be limited in small structures of the brain since the
4
5 volumes are smaller and there is also a lower signal-to-noise ratio in preterm
6
7 children. To minimize this we used only high quality MRI. To guide segmentation we
8
9 used a larger number of tissue probability maps from preterms³⁵ with an extra class
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11 tissue map for background, to provide a better modelling of the cerebrospinal fluid
12
13 and other non-brain voxels and also to aid further tissue classification. Visual-motor
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15 integration was assessed with the main Beerys VMI test, but did not include the
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17 supplementary tests of visual perception and motor coordination which could have
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19 enabled us to distinguish between visual perception and fine motor function with
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21 regard to the VMI function. We did not adjust for any diagnosis of autism or ADHD,
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23 which are reported to be common in children born extremely preterm⁵⁴ and have
24
25 been linked to altered brain development in preterms^{36 55} Finally, we were not able to
26
27 include a control group of children born at term.
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29

30 *Conclusion*

31
32 In summary, this study found positive correlations between VMI performance, fine
33
34 motor skills and brain volumes at term-equivalent age in regions that were already
35
36 known to be involved in these functions. To our knowledge, this is the first study to
37
38 examine the relationship between neonatal brain volumes and VMI and fine motor
39
40 skills at the age of 6.5 years in a population-based cohort of children born EPT.
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42 Further studies including larger sample sizes are needed to confirm our results, to
43
44 explore the relationships between the underlying visual and motor modalities and
45
46 VMI in greater depth, and to examine the potential use of early regional brain
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48 volumes as imaging biomarkers related to VMI and fine motor skills. Since it has
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50 been reported that early interventions can improve VMI in general school populations
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3 ⁵⁶ as well as in children born preterm ⁵⁷ , a possibility of early identification of children
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5 at risk could diminish the impact of preterm birth on these functions.
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8 **Ethical approval:** All procedures performed in studies involving human participants
9
10 were in accordance with the ethical standards of the institutional and/or national
11
12 research committee and with the 1964 Helsinki declaration and its later amendments
13
14 or comparable ethical standards.
15

16
17 **Informed consent:** Informed consent was obtained from the parents of all individual
18
19 participants included in the study.
20
21

22 **Author's contributions:**

23
24 J Bolk designed the study, collected data, performed analyses, interpreted the data,
25
26 drafted and revised the manuscript and approved the final version.
27

28
29 N Padilla designed the study, collected data, performed analyses, interpreted the
30
31 data, revised the manuscript and approved the final version.
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33
34 L Broström collected data, interpreted data, revised the manuscript and approved the
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36 final version.
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39 L Forsman collected data, interpreted data, revised the manuscript and approved the
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41 final version.
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44 K Hellgren collected data, interpreted data, revised the manuscript and approved the
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46 final version.
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48
49 U Åden designed the study, collected data, interpreted the data, revised the
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51 manuscript and approved the final version
52

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54
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56
57 possible.
58

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Abbreviations: *Cerebral palsy (CP), Sum of grey and white matter excluding cerebrospinal fluid (CPAR), Extremely Preterm Born (EPT), Gestational age (GA), Magnetic Resonance Imaging (MRI), Movement Assessment Battery for Children-2 (M-ABC), Standard Deviation (SD), Visual-motor integration (VMI)*

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8 **Figure 1.** Study population
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10 **Figure 2.** Illustrations of partial correlations between neonatal brain volumes, visual-
11 motor integration and fine motor skills (assessed by manual dexterity scores on the
12 Movement Assessment Battery for Children-2) at 6.5 years of age, using plots of
13 residuals. Analyses are adjusted for total cerebral parenchyma (grey matter plus
14 white matter) and sex. (A) Correlations between the volume of the precentral gyrus
15 and visual-motor integration scores. (B-E) Correlations between the volumes of the
16 cerebellum, brainstem, precentral gyrus, grey matter and fine motor skills. Results
17 are presented without correction for multiple comparisons.
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28 **Supplementary Figure1.** Atlas overlaid on the sagittal, coronal and axial T1-
29 weighted images from a single preterm child. Individual anatomical regions are color
30 coded.
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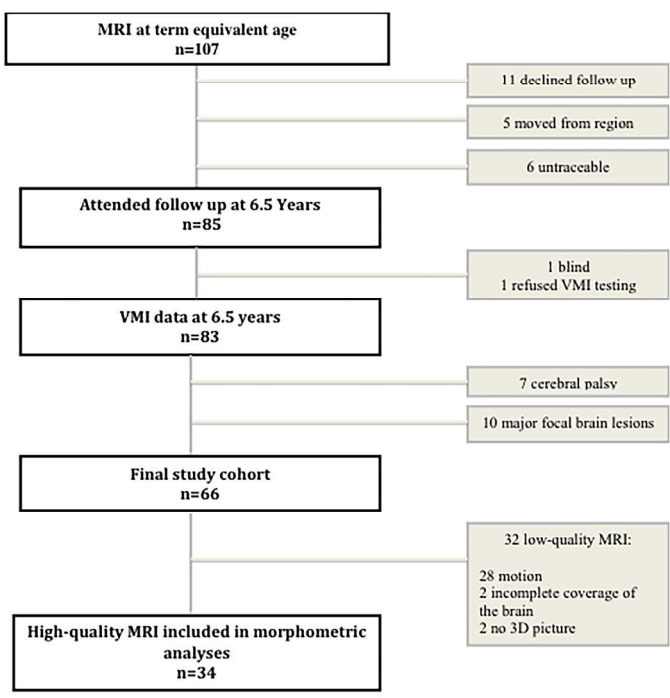


Figure 1. Study population

515x387mm (300 x 300 DPI)

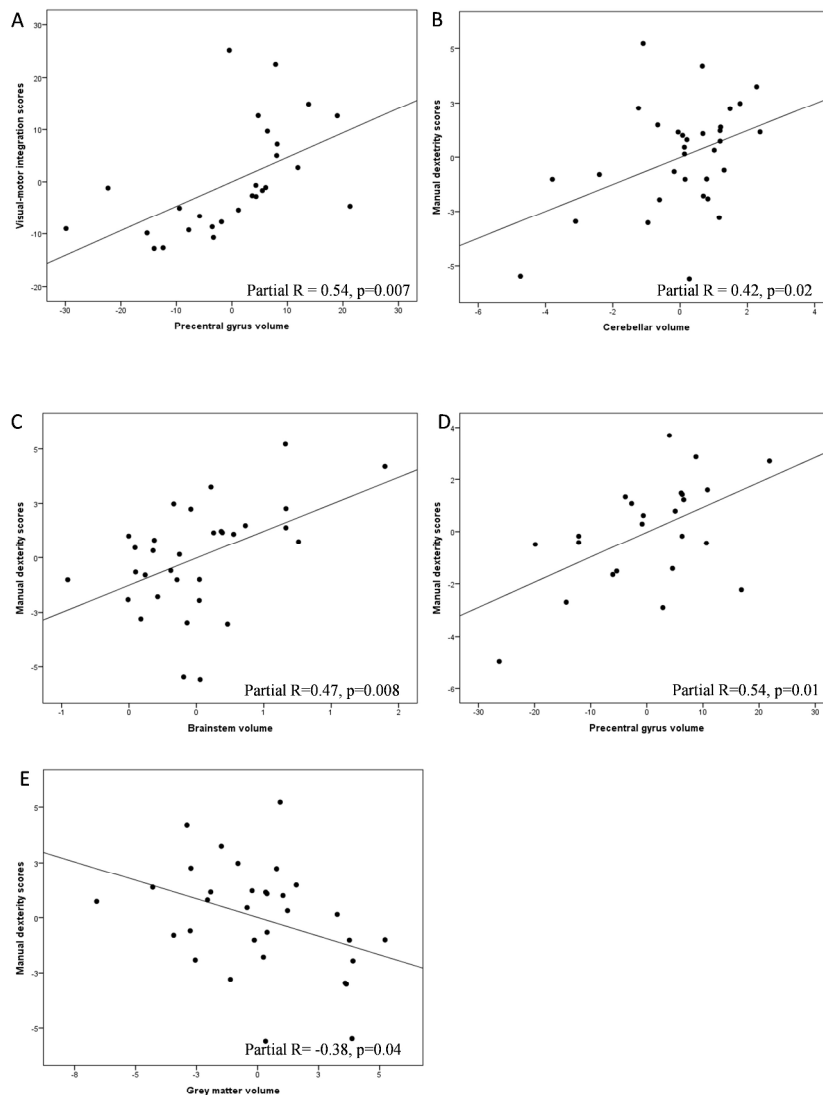
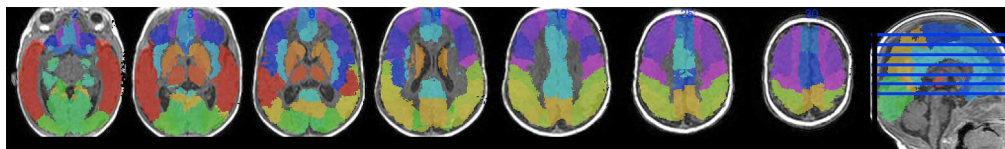


Figure 2. Illustrations of partial correlations between neonatal brain volumes, visual-motor integration and fine motor skills (assessed by manual dexterity scores on the Movement Assessment Battery for Children-2) at 6.5 years of age, using plots of residuals. Analyses are adjusted for total cerebral parenchyma (grey matter plus white matter) and sex. (A) Correlations between the volume of the precentral gyrus and visual-motor integration scores. (B-E) Correlations between the volumes of the cerebellum, brainstem, precentral gyrus, grey matter and fine motor skills. Results are presented without correction for multiple comparisons.

335x421mm (300 x 300 DPI)

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Supplementary Figure 1. Atlas overlaid on the sagittal, coronal and axial T1-weighted images from a single preterm child. Individual anatomical regions are color coded.

700x101mm (300 x 300 DPI)

For peer review only

Supplementary Table 1. Characteristics of the children born at gestational age <27 weeks with or without high quality MRI

	High quality MRI n=34	Low quality MRI n=32	<i>p</i>
Gestational age at birth, weeks, median (range)	25.85 (23.4-26.6)	25.45 (23.4-26.6)	0.16
Birth weight, grams, mean (SD)	857 (154)	820 (47)	0.33
Gender, girls/boys, n	15/19	14/18	1.00
Small for gestational age, n	1	3	0.35
Prenatal steroids, n	32	28	0.42
Premature rupture of the membranes, n	10	9	1.00
Cesarean section, n	16	16	1.00
Sepsis, n	24	27	0.24
Days of mechanical ventilation, median (range)	3 (0-37)	11 (0-55)	0.04
Postnatal steroids, n	4	7	0.33
Bronchopulmonary Dysplasia, oxygen at 36 weeks, n	12	14	0.62
Necrotizing enterocolitis, n	1	5	0.10
Patent ductus arteriosus, ligation, n	9	11	0.60
Laser treatment for retinopathy of prematurity, n	2	6	0.14
Intraventricular hemorrhage grade I-II, n	10	13	0.44
Mild white matter abnormality, n	18	12	0.09
Gestational age at MRI, weeks, median (range)	40.79 (39.14-45.28)	40.28 (39.14-43.28)	0.08
Age at 6.5 year assessment, months, median (range)	77.20 (75.29-80.18)	77.23 (76.03-86.33)	0.59
VMI standard score, mean (SD)	94 (10)	91 (9)	0.20
M-ABC-2 manual dexterity score, mean (SD)	8 (2)	7 (3)	0.68

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3 All children were without cerebral palsy, focal brain lesions or severe white matter
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5 abnormalities. SD = Standard deviation, MRI = Magnetic Resonance Imaging, VMI=Visual-
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7 motor integration, M-ABC-2=Movement Assessment Battery for Children-2
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Supplementary Table 2. Characteristics of the children born at gestational age <27 weeks with and without atlas segmentation data.

	Atlas segmentation data n=26	No atlas segmentation data n=40	<i>p</i>
Gestational age at birth, weeks, median (range)	26.85 (23.4-26.6)	25.50 (23.4-26.6)	0.28
Birth weight, grams, mean (SD)	874 (153)	817 (146)	0.13
Gender, girls/boys	13/13	16	0.46
Small for gestational age, n	0	4	0.15
Prenatal steroids, n	25/26	35	0.39
Premature rupture of the membranes, n	7	12	1.00
Cesarean Section, n	10	22	0.22
Sepsis, n	17	34	0.08
Days of mechanical ventilation, median (range)	3 (0-36)	10 (0-55)	0.04
Postnatal steroids, n	3	8	0.51
Bronchopulmonary Dysplasia, oxygen at 36 weeks, n	10	16	1.00
Necrotizing enterocolitis, n	0	6	0.07
Patent ductus arteriosus, ligation, n	7	13	0.79
Laser treatment for retinopathy of prematurity, n	1	7	0.13
Intraventricular hemorrhage grade I-II, n	7	16	0.30
Mild white matter abnormality, n	16	14	0.09
Gestational age at MRI, weeks, median (range)	40.93 (39.71-43.28)	40.36 (39.14-45.28)	0.18
Age at 6.5 year assessment, months, median (range)	77.16 (75.29-80.20)	77.23 (76.03-86.33)	0.21
VMI standard score, mean (SD)	91.69 (14.14)	89.82 (11.71)	0.87

M-ABC-2 manual dexterity score, mean (SD)	7 (2)	8 (3)	0.38
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All children were without cerebral palsy, focal brain lesions or severe white matter abnormalities.

SD = Standard deviation, MRI = Magnetic Resonance Imaging, VMI=Visual-motor integration, M-ABC-2=Movement Assessment Battery for Children-2

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Supplementary Table 3. Correlations between brain volumes at term equivalent age, visual-motor integration and fine motor skills scores at 6.5 years in children born at GA <27 weeks.

Brain region	Visual-motor integration		Fine motor skills	
	Correlation coefficient (partial r)	p	Correlation coefficient (partial r)	p
Grey matter	0.05	0.77	-0.38	0.04
White matter	-0.33	0.07	0.11	0.57
Deep grey matter	0.02	0.93	0.05	0.79
Cerebellum	0.24	0.19	0.42	0.02
Brain stem	0.08	0.66	0.47	0.008
Frontal lobe	-0.11	0.61	-0.19	0.40
Temporal lobe	-0.10	0.63	-0.12	0.61
Parietal lobe	-0.33	0.12	-0.22	0.32
Occipital lobe	0.18	0.40	0.26	0.24
Central Region	0.35	0.09	0.30	0.17
Networks				
Visual network				
Superior occipital gyrus	0.23	0.28	0.39	0.07
Middle occipital gyrus	0.12	0.59	0.06	0.78
Inferior occipital gyrus	-0.26	0.22	-0.21	0.35
Calcarine cortex	-0.24	0.27	-0.01	0.97
Cuneus	0.27	0.20	0.20	0.37
Lingual gyrus	-0.13	0.54	-0.01	0.67
Motor network				
Precentral gyrus	0.54	0.007	0.54	0.01
Frontal medial	0.005	0.99	-0.05	0.83
Supplementary motor area	-0.03	0.89	-0.19	0.40
Sensory network				
Postcentral gyrus	0.07	0.75	0.17	0.45
Salience network				
Insula	-0.001	0.99	-0.08	0.73
Anterior cingulate gyrus	0.09	0.67	0.10	0.65
Thalamus	-0.04	0.87	0.11	0.62
Amygdala	-0.16	0.45	-0.23	0.31
Default mode network				
Precuneus	-0.26	0.22	-0.05	0.84
Angular_gyrus	0.26	0.21	-0.17	0.45
Hippocampus	-0.08	0.72	-0.11	0.63
Subcortical regions				
Subcortical grey matter, total	-0.10	0.63	-0.04	0.86
Pallidum	0.01	0.99	0.07	0.76

Caudate	-0.04	0.85	-0.09	0.70
Putamen	-0.26	0.23	0.06	0.79

All children are without cerebral palsy or major brain lesions. Results from Pearson's partial correlation, adjusted for total cerebral parenchyma (total cortical grey and white matter) and sex. Central region = precentral and postcentral gyri, rolandic operculum bilaterally. Results are presented without correction for multiple comparisons.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-10
		(b) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-11
Bias	9	Describe any efforts to address potential sources of bias	10-12
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	10
		(b) Describe any methods used to examine subgroups and interactions	10
		(c) Explain how missing data were addressed	10-11
		(d) If applicable, explain how loss to follow-up was addressed	-
		(e) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7,12,Figure 1
		(b) Give reasons for non-participation at each stage	7, 12, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8,11
		(b) Indicate number of participants with missing data for each variable of interest	11, Figure 1
		(c) Summarise follow-up time (eg, average and total amount)	7, 12, Supplementary Table 1, Supplementary Table 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12 Figure 2
		(b) Report category boundaries when continuous variables were categorized	-
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplementary Table 1, Supplementary Table 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	11,12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17,18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3-4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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4 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE
5 checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
6 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.
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