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## Relations between brain volumes, neuropsychological assessment and parental questionnaire in prematurely born children

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**Abstract** The objective of this study is to assess the relationship between brain volumes at term equivalent age and neuropsychological functions at 5 years of age in very low birth weight (VLBW) children, and to compare the results from a neuropsychological assessment and a parental questionnaire at 5 years of age. The study group included a regional cohort of 97 VLBW children and a control group of 161 children born at term. At term equivalent age, brain magnetic resonance imaging (MRI) was performed on the VLBW children, and analysed for

total and regional brain volumes. At 5 years of age, a psychologist assessed the neuropsychological performance with NEPSY II, and parents completed the Five to fifteen (FTF) questionnaire on development and behaviour. The results of the control group were used to give the age-specific reference values. No significant associations were found between the brain volumes and the NEPSY II domains. As for the FTF, significant associations were found between a smaller total brain tissue volume and poorer executive functions, between a smaller cerebellar volume and both poorer executive functions and motor skills, and, surprisingly, between a larger volume of brainstem and poorer language functions. Even after adjustment for total brain tissue volume, the two associations between the cerebellar volume and the FTF domains remained borderline significant ( $P = 0.05$ ). The NEPSY II domains *Executive Functioning*, *Language* and *Motor Skills* were significantly associated with the corresponding FTF domains. In conclusion, altered brain volumes at term equivalent age appear to affect development still at 5 years of age. The FTF seems to be a good instrument when used in combination with other neuropsychological assessment.

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**Keywords** VLBW · Brain volumes · Outcome ·  
NEPSY II · FTF

### Abbreviations

|          |  |
|----------|--|
| <i>b</i> | Estimated regression coefficient       |
| CP       | Cerebral palsy                         |
| FE       | Field echo                             |
| FTF      | Five to fifteen                        |
| MRI      | Magnetic resonance imaging             |
| <i>P</i> | <i>P</i> value                         |
| SGA      | Small birth weight for gestational age |

|      |                       |
|------|-----------------------|
| SE   | Standard error        |
| TE   | Time echo             |
| TR   | Time repetition       |
| US   | Ultrasound            |
| VLBW | Very low birth weight |

## Introduction

Prematurely born children exhibit more neuropsychological deficits than those born at term. Executive functions [5, 9, 10], attention [11, 12, 20, 31, 37], memory functions [10, 11, 20, 33], visuomotor and visuospatial functions [11, 12, 20, 33], as well as language functions [11, 20, 33, 40] have been found to be affected by a preterm birth. Neuropsychological functions are usually studied using neuropsychological/psychological tests and test batteries administrated by a psychologist. Parental questionnaires have, however, also appeared valid in developmental assessment [19, 35]. Parents though tend to report more concerns on the development of the child than the formal neuropsychological assessment shows [19].

The significance of altered brain volumes on preterm children's development has been at the centre of interest in several studies. Altered volumes at term equivalent age have been shown to associate with an impaired development at 1 year [4, 13], at 18 months [4], at 18–20 months [22], and at 2 years of corrected age [6, 28, 29, 34, 42]. So far, there have been no previous studies on the relationship between the brain volumes at term equivalent age and the outcome beyond 2 years corrected age.

The present study focuses on the development of a regional cohort of very low birth weight (VLBW) children at 5 years of age. The aims of the study were to evaluate the relationship between (1) the total and regional brain volumes at term equivalent age and the neuropsychological performance at 5 years of age, and (2) the results from the psychological examinations and parental questionnaires in the assessment of the neuropsychological performance at 5 years of age. We hypothesized that (1) decreased brain volumes associate with a less optimal neuropsychological performance, and that (2) parents identify the same deficits that can be found in neuropsychological examination.

## Methods

### Participants

This study is a part of a multidisciplinary, longitudinal research project PIPARI (development and functioning of

very low birth weight infants from infancy to school age). The study sample consisted of VLBW children born in 2001–2003 at Turku University Hospital. Inclusion criteria for this study were (1) a birth weight of <1,501 g and a gestational age of <37 weeks, (2) a Finnish speaking family, and (3) a family residing inside the hospital catchment area. Excluded were the infants who (1) died during the neonatal period ( $n = 22$ ), or (2) had a major congenital anomaly or a recognized syndrome ( $n = 1$ ). Out of the 103 children eligible for the study, six families withdrew from it before the child was 5 years old. The final study group consisted of 97 children. In the analyses the total number of children varies as data on some of the children were missing, as described in detail in “Results”.

A control group for the neuropsychological tests and the questionnaire consisted of healthy full-term infants born in 2001–2003 at the same hospital. The control group was recruited by asking the first boy and the first girl born on each week to take part in the study. If the parents refused, the next boy/girl was recruited. Inclusion criteria for the controls were (1) birth weight  $> -2.0$  SD according to the age and gender specific Finnish growth charts, and gestational age  $\geq 37$  weeks at birth, (2) no admission to neonatal care during the first week of life, (3) a Finnish speaking family, and (4) a family residing inside the hospital catchment area. We excluded the control infants with (1) a congenital anomaly or syndrome, or (2) a self-reported maternal use of illicit drugs or alcohol during the pregnancy. Of the 169 controls who were eligible for the study, eight families withdrew from the study before the child was 5 years old. The final group consisted of 161 children. In the analyses, the total number of children varies as data on some of the children were missing, as described in detail in “Results”.

A written consent was obtained from all the parents after they were given oral and written information. The PIPARI Study protocol was approved by the Ethics Review Committee of the Hospital District of the South-west Finland in December 2000.

### Serial cranial ultrasound

Brain pathology classification based on cranial ultrasound (US) was used as a background variable. The examinations in the neonatal intensive care unit were performed on all preterm infants at 3–5 days, at 7–10 days, at 1 month of age and, thereafter, monthly until discharge from hospital and at term equivalent age. The US examinations were performed as described in Reiman et al. [26]. The infants were categorized into three groups according to the most pathological finding in the brain US examinations: (1) normal, (2) mildly abnormal, and (3) severely abnormal. The division into these groups was done according to Rademaker et al. [25].

## Magnetic resonance imaging of the brain

Magnetic resonance imaging (MRI) of the brain was performed on all the VLBW infants at term equivalent age on the same day as the US examination. The imaging took place during a postprandial sleep without a pharmacological sedation or anaesthesia and ear protection was used (3 M disposable ear plugs 1,100, 3 M, Brazil; Würth Hearing protector Art.-Nr. 899 300 232, Würth, Austria). An open 0.23 T Outlook GP (Philips Medical Inc., Vantaa, Finland) was used.

For the volume measurements, we obtained a T1-weighted field echo (FE) sequence with a time repetition (TR) of 30 ms, a time echo (TE) of 10 ms, a flip angle of 45°, a slice thickness of 5 mm, a field of view of 220 × 220 mm<sup>2</sup> and a matrix of 256 × 256 in the coronal plane. The sequence was optimized relative to the field strength.

The postacquisition volume measurements were performed on a GE workstation (GE AW1.0, GE Medical Systems, Milwaukee, USA) by one neuroradiologist. The coronal T1-weighted images were loaded into Functool 1.0.post-processing software (GE Medical Systems, Milwaukee, USA). The volume measurement was manually performed separating the cerebrospinal fluid and the skull from brain tissue image by image. The anatomical differentiation of the brain areas was based both on the anatomical landmarks and on the signal intensity differences of the brain structures. In addition to the total brain volume (total brain volume minus ventricle volumes), the regional brain volumes were measured including the cerebral volume, the cerebellar volume, the frontal lobe volume, the combined volume of the medulla oblongata and the pons, and the combined volume of the basal ganglia and thalami. The cerebellar volume included the cerebellar hemispheres, the vermis, and the cerebellar peduncles. The frontal lobes included the area anterior to the central sulcus. The pons and medulla oblongata were delineated together with the upper border of this area being the lower border of mesencephalon, and the lower border the junction between the medulla oblongata and the cervical spinal cord. The basal ganglia and thalami were measured as a block and the anatomical border between these basal grey matter nuclei and unmyelinated deep white matter was easily delineated by visual inspection. The medial border of the basal ganglia and thalami was formed by the third ventricle, the lateral border was formed by the external capsule and the inferior border was formed by the upper border of the mesencephalon. The neuroradiologist was blinded to both the clinical information and the result of the ultrasound examination of the infant.

The brain volume measurements of all the children in this study were performed by one neuroradiologist. The

reproducibility of these measurements was assessed by repeated brain volume measurement of 20 children, performed by another neuroradiologist who was blinded for the results of the first volume measurement.

## NEPSY II

The neuropsychological performance was evaluated at 5 years chronological age (+0–2 months) by a psychologist using the Finnish standardization edition of NEPSY II [17, 18]. Age-appropriate subtests were selected from the NEPSY II to form a comprehensive set of tests that represent various domains of neurocognitive development. The selected subtests assess attention, executive functioning, language functions, memory functions, and visuomotor and visuospatial functions, and provide a profile of neuropsychological functions. As the scoring instructions for the NEPSY II were not yet finalized at the time of the study, the administration and scoring rules differed somewhat from those of the published version. These differences are noted below. The subtests are described after Korkman et al. [17] (pp. 21–23).

### *Executive functioning*

The *auditory attention* subtest, part A, is aimed at assessing the selective auditory attention and the ability to sustain it. The test material is a sheet with circles in four different colours and an audiotape presenting short, isolated words for 180 s. The child listens to the tape and touches the red circle when he or she hears the target word “red”, which is presented with irregular intervals amidst other words. The score used in this study was received by subtracting the number of commission errors from the number of correct responses.

The *visual attention* subtest is aimed at assessing selective visual attention. The child is given an A3 size sheet on top of which there are two faces in line drawings. The child is instructed to mark the similar faces among dissimilar ones on the page. Performance time, errors and omissions are combined in the test score. This subtest is included only in the Finnish NEPSY II. It is a modification of a subtest from the earlier version of the NEPSY, part Faces [16].

The *inhibition* subtest is aimed at assessing the ability to inhibit automatic responses. Two parts of this subtest were administered. In the first part, the child looks at a series of black and white shapes and is asked to name them as fast as possible. In the second part, the child should name them in an alternate way as fast as possible, saying “circle” for “square” and “square” for “circle”. The score used in this study

was a combination score of Total Score and Total Completion Time from the Switching Condition (second part).

### Language

The *speeded naming* subtest is aimed at assessing rapid semantic access to and production of names of basic colours, shapes, and sizes. The child was told to name arrays of figures according to their colours, shapes (square or circle), and sizes (small or large) as quickly as possible. In this study, the size/colour/shape naming condition was administered which is done only from the age of 7 in the final NEPSY II version, but the scoring was more lenient than in the final version. The child was, for example, allowed to use the word “ball” in addition to “circle”.

The *comprehension of instructions* subtest is aimed at assessing the ability to receive and process oral instructions of increasing syntactic complexity. The test material consists of a sheet with rabbits or with circles and crosses in different colours. The instructions may, for example, indicate a sequence of figures and the child is asked to point to appropriate stimuli in the appropriate order.

The *phonological processing* subtest is aimed at assessing phonemic awareness. Two parts of the subtest were administered. In the first part, the child needs to identify words when the examiner presents segments of the words apart. In the second part the child is first asked to repeat a word and then form a new word by omitting a syllable or a phoneme, or by substituting a phoneme for another.

### Memory

The *narrative memory* subtest is aimed at assessing memory for logical verbal material under free and cued recall. The child listens to a story and is then asked to repeat it (Free Recall condition). The child is then asked questions concerning details missing from his or her recall of the story (Cued Recall condition).

The *memory for designs* subtest is aimed at assessing spatial memory for novel visual material. The child is shown a series of non-figural designs placed on a grid, which are removed from view after each presentation. After each presentation the child selects the appropriate designs from a set of cards and places them on an empty grid in the same location as was shown. The child was instructed on how many cards should be placed on the grid but was not penalized for putting too many.

The *word list interference* subtest is aimed at assessing verbal working memory. The child listens to pairs of word series, going from short series to longer series. In each pair, the first series of words is presented first and the child repeats it. Thereafter, the second series is presented and the child repeats it. Finally, the child recalls both series again, in the order of presentation. The score used in this study was the Recall Total Score.

### Motor skills

The *visuomotor precision* subtest is aimed at assessing graphomotor speed and accuracy. The child is asked to draw a line inside of a curvilinear track representing the route of a car as precisely and as quickly as possible. Only the car item was used. The score used in this study was a combination score of the total errors and total completion time.

The *design copy* subtest is aimed at assessing motor and visual–perceptual skills associated with the ability to copy two-dimensional geometric figures. The child is asked to copy figures displayed one at a time. Only items 1–11 were included. No discontinue rule was applied.

### Five to fifteen

A Five to fifteen (FTF) questionnaire [8, 14, 19, 35] was sent to the parents 1 month prior to the fifth birthday of the child. The FTF is a validated questionnaire with 181 questions on different areas of the development and behaviour of children. Questions that are not appropriate for children under school age were removed (items 16, 48 to 51, 63, 64, and 93 to 105). The questionnaire items have been listed elsewhere [14]. The following domains were included: *Executive functioning* (including attention, impulsivity and ability to plan and organize), *Language*, *Memory*, and *Motor skills*.

### Statistical analysis

Age corrected scaled scores (range 1–19 with a median of 10) were created for the NEPSY II and the FTF from the subtest raw scores of the control group. Non-parametric methods were used to create scaled scores as recommended in the methodological article of Solberg [32]. The scale was based on percentiles that were classified to correspond to distribution of common standard test scores with a mean of 10 and SD of 3. However, the distribution of scaled scores might be heavy-tailed due to the discrete nature of raw scores. Because the resulting distributions were clearly bell-shaped, robust parametric analyses were nevertheless

undertaken. A score of eight or above was considered as normal performance, in accordance with the NEPSY II test manual [17].

In order to reduce the number of variables in the NEPSY II, domains were created of the subtests. In the comparison of the NEPSY II and the FTF the following combinations were used: a combined score for the NEPSY II subtests *auditory attention*, *visual attention* and *inhibition* was compared with scores for the FTF domain *Executive functioning*; a combined score for the NEPSY II subtests *speeded naming*, *comprehension of instructions* and *phonological processing* was compared with scores for the FTF domain *Language*; a combined score for the NEPSY II subtests *narrative memory*, *memory for designs* and *word list interference* was compared with scores for the FTF domain *Memory*; and a combined score for the NEPSY II subtests *visuomotor precision* and *design copy* was compared with scores for the FTF domain *Motor skills*. The mean value of the scores for the NEPSY II subtests in each domain was considered as a score for the domain.

As the FTF was missing from 11% of the VLBW children and from 20% of the control children, we analysed if the responders were representative of the study population regarding gender, birth weight, parental education and scores of the domains in the NEPSY II. The responders and non-responders were compared using the Chi-square test or the Fisher's exact test, as appropriate, for categorical variables and independent samples *t* test for continuous variables. Independent samples *t* test was also used to compare test results between preterm and full-term infants.

The associations between the brain volumes and outcome variables (NEPSY II, FTF) were studied using a multiple regression analysis. The background variables included in the statistical analysis of the associations between the brain volumes and neuropsychological functioning were birth weight, gestational age, small birth weight for gestational age (SGA, birth weight  $\leq -2$  SD according to the reference values for the Finnish population), gender, mother's and father's education (in three categories according to the length of education:  $\leq 9$  years, 10–12 years,  $>12$  years), respectively, and brain pathology based on the cranial US findings (three groups: normal, mildly abnormal, and severely abnormal). Diagnostic plots were produced to ensure that normality and other assumptions of the analyses were reasonably satisfied. As a result of these checks, skewed variables (volumes of ventricles and brain stem) were log transformed and a part of the results are presented with and without outlying observations. The intraclass correlation coefficient (ICC [1, 2]) was calculated to describe the interobserver

reliability [30] between two neuroradiologists regarding the volume measurements.

Background variables included in the multiple regression analysis when associations between the neuropsychological tests and the questionnaire were assessed, were gender, and mother's and father's education as above. The statistical analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC). The values were considered statistically significant if the *P* value was  $<0.05$ .

## Results

Regarding missing data in the VLBW group, information about mother's education was not available for one child and about father's education for one child. Because of motion artefacts during the imaging, information from volumetric analysis was missing from two children. Six children could not be assessed with the NEPSY II because of severe developmental problems (described in detail below), and five children did not participate in the NEPSY II assessment at all or within 2 months from the fifth birthday. Of the children who were assessed with NEPSY II, some did not have a result in every subtest due to lack of cooperation or concentration, inability to understand the instructions, or tiredness. The number of missing results were as follows: *auditory attention*,  $n = 4$ , *visual attention*,  $n = 3$ , *inhibition*,  $n = 3$ , *speeded naming*,  $n = 6$ , *comprehension of instructions*,  $n = 1$ , *phonological processing*,  $n = 0$ , *narrative memory*,  $n = 4$ , *memory for designs*,  $n = 4$ , *word list interference*,  $n = 6$ , *visuomotor precision*,  $n = 0$ , *design copy*,  $n = 6$ . In the domain scores, missing data were replaced with mean value of the remaining subtests in the domain. The FTF was missing from 11 VLBW children.

Information about neurodevelopmental impairments had been collected in the PIPARI study. Neurodevelopmental impairments were stated in 15 (15%) children. Of these, seven children had only cerebral palsy (CP), two had only a hearing impairment (defined as a need for hearing aid), two of the children whose intelligence could be assessed had only a cognitive impairment (intelligence quotient below 70,  $-2$  SD), one had both CP and a hearing impairment, and three had both CP and a cognitive impairment. None of the children was blind. Of these, 15 children with neurodevelopmental impairments, five did not undergo the examination with NEPSY II (of these five, one had a hearing impairment, one had a cognitive impairment, one had CP and a hearing impairment, and two had CP and a cognitive impairment). One child could not be assessed with NEPSY II due to severe attention deficits.

In the control group, information about mother's education was missing from 22 children and about father's education from 27 children. Twelve children did not participate in the NEPSY II assessment and the FTF was missing from 32 children.

The drop-out analysis of the FTF questionnaire of the VLBW children showed that the FTF was significantly more often returned by parents with higher maternal ( $P = 0.002$ ) and paternal ( $P = 0.002$ ) education. A lower birth weight was also associated with a higher response rate in the VLBW group ( $P = 0.048$ ). As for the control group, FTF was returned from more fathers with high education ( $P = 0.018$ ).

The background variables of the participants are presented in Table 1. The mean values of the brain volumetric findings, the results of the NEPSY II and of the FTF are presented in Table 2. The test scores of the NEPSY II and the FTF differed significantly in all domains. Intraclass correlation coefficients for the volume measurements ranged from 0.93 to 0.99, except for the volume of brainstem for which the intraclass correlation coefficient was 0.78.

The results from the analysis of the associations between the brain volumetric findings and the outcome measures were controlled for background variables. No significant

associations were found between the brain volumes and the NEPSY II domains. The lowest  $P$  values emerged for the volume of brainstem and the domain *Language* ( $P = 0.072$ , estimated regression coefficient,  $b = -1.183$ , standard error,  $SE = 0.648$ ), the volume of the ventricles and the domain *Memory* ( $P = 0.090$ ,  $b = -0.698$ ,  $SE = 0.406$ ), and the cerebellar volume and the domain *Motor skills* ( $P = 0.121$ ,  $b = 0.116$ ,  $SE = 0.074$ ). The rest of the  $P$  values ranged from 0.137 to 0.997. As for the FTF, a smaller total brain tissue volume was significantly associated with poorer scores in the FTF domain *Executive functioning* ( $P = 0.042$ ,  $b = 0.024$ ,  $SE = 0.012$ ) and a larger volume of brainstem with poorer scores in the FTF domain *Language* ( $P = 0.002$ ,  $b = -4.020$ ,  $SE = 1.276$ ). In addition, a smaller cerebellar volume was significantly associated with poorer scores in the FTF domains *Executive functioning* ( $P = 0.007$ ,  $b = 0.254$ ,  $SE = 0.092$ ) and *Motor skills* ( $P = 0.013$ ,  $b = 0.261$ ,  $SE = 0.102$ ).

The analyses of associations between brain volumes and outcome measures were repeated excluding the nine children with severely abnormal brain findings. The significant associations between the cerebellar volume and the FTF domains *Executive functioning* and *Motor skills*, and between the volume of brainstem and the FTF domain *Language*, remained significant. In addition, the association between the brainstem volume and the NEPSY II domain *Language* reached significance ( $P = 0.029$ ,  $b = -1.328$ ,  $SE = 0.596$ ), and the association between the total brain tissue volume and the FTF domain *Executive functioning* was no longer significant ( $P = 0.089$ ,  $b = 0.023$ ,  $SE = 0.013$ ).

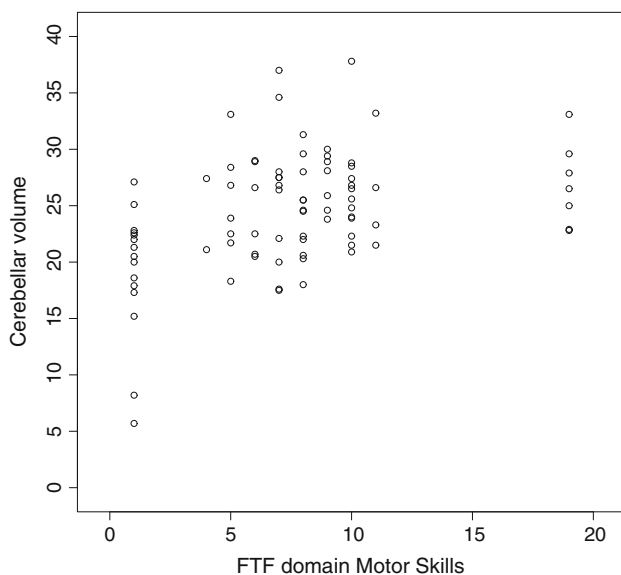
As can be seen from Fig. 1, there were two outlying observations with the smallest cerebellar volumes. When these two children were excluded from the analyses of the associations between the volume of cerebellum and the FTF domains, only the association between the smaller cerebellar volume and poorer scores in the *Motor skills* domain remained significant ( $P = 0.043$ ,  $b = 0.237$ ,  $SE = 0.115$ ). The two children who had the smallest cerebellar volumes were among those who could not be assessed with the NEPSY II because of a severe handicap. To delineate the focal effects more clearly, we also repeated the analyses of the significant associations between the cerebellar volume and the FTF domains, using the proportion of cerebellar volume of the total brain tissue volume, instead of the absolute volume, and adjusting for the total brain tissue volume in addition to the other covariates. Accordingly, the  $P$  value for the association between the cerebellar volume and the FTF domain *Executive functioning* was 0.052 ( $b = 0.771$ ,  $SE = 0.391$ ), and the  $P$  value for the association between the cerebellar volume and the FTF domain *Motor skills* 0.050 ( $b = 0.869$ ,  $SE = 0.436$ ).

**Table 1** The background variables of the very low birth weight (VLBW) children and of the control children

| Background variables                                       | VLBW children                         | Control children                      |
|--|---------------------------------------|---------------------------------------|
| Gender   |                                       |                                       |
| Boy ( $n$ )  | 50 (52%)                              | 80 (50%)                              |
| Girl ( $n$ )   | 47 (48%)                              | 81 (50%)                              |
| Birth weight (g), mean (SD)<br>[min, max]                  | 1,040 (273)<br>[400, 1,500]           | 3,644 (446)<br>[2,570, 4,980]         |
| Gestational age<br>(weeks + days), mean (SD)<br>[min, max] | 28 + 2 (2 + 5)<br>[23 + 0,<br>35 + 6] | 40 + 0 (1 + 1)<br>[37 + 1,<br>42 + 2] |
| Small for gestational age (SGA)                            |                                       |                                       |
| Yes ( $n$ )  | 35 (36%)                              |                                       |
| No ( $n$ )   | 62 (64%)                              |                                       |
| Brain pathology  |                                       |                                       |
| Normal ( $n$ )   | 45 (46%)                              |                                       |
| Mildly abnormal ( $n$ )                                    | 43 (44%)                              |                                       |
| Severely abnormal ( $n$ )                                  | 9 (9%)                                |                                       |
| Mother's education (years)                                 |                                       |                                       |
| $\leq 9$ ( $n$ )   | 12 (13%)                              | 7 (5%)                                |
| 10–12 ( $n$ )  | 25 (26%)                              | 54 (39%)                              |
| >12 ( $n$ )  | 59 (61%)                              | 78 (56%)                              |
| Father's education (years)                                 |                                       |                                       |
| $\leq 9$ ( $n$ )   | 10 (10%)                              | 15 (11%)                              |
| 10–12 ( $n$ )  | 56 (58%)                              | 58 (43%)                              |
| >12 ( $n$ )  | 30 (31%)                              | 61 (46%)                              |

**Table 2** Mean values (SD) [min, max] of brain volumetric findings, results in NEPSY II and results in five to fifteen (FTF) in the very low birth weight (VLBW) children and in the control children, and comparison (*P* value) of results in the NEPSY II and FTF

|                                | VLBW children               | Control children       | <i>P</i> |
|--------------------------------|-----------------------------|------------------------|----------|
| <b>Brain volumes</b>           |                             |                        |          |
| Total brain tissue (ml)        | 391.7 (47.4) [280.2, 508.9] |                        |          |
| Ventricles (ml)                | 20.4 (27.3) [3.8, 222.9]    |                        |          |
| Cerebrum (ml)                  | 359.7 (44.5) [258.6, 465.7] |                        |          |
| Frontal lobes (ml)             | 134.3 (22.8) [93.2, 194.1]  |                        |          |
| Basal ganglia and thalami (ml) | 26.0 (5.2) [13.3, 42.8]     |                        |          |
| Cerebellum (ml)                | 24.4 (5.1) [5.7, 37.8]      |                        |          |
| Brain stem (ml)                | 7.6 (2.8) [3.3, 14.9]       |                        |          |
| <b>NEPSY II</b>                |                             |                        |          |
| Executive functioning          | 8.6 (2.0) [3.3, 13.0]       | 9.9 (2.0) [3.5, 15.0]  | <0.001   |
| Language                       | 8.9 (2.0) [4.0, 14.3]       | 10.0 (2.2) [4.0, 15.3] | 0.001    |
| Memory                         | 8.7 (2.5) [3.5, 14.0]       | 10.0 (1.9) [4.7, 17.7] | <0.001   |
| Motor skills                   | 8.3 (2.6) [2.0, 13.5]       | 9.9 (2.5) [3.0, 16.0]  | <0.001   |
| <b>FTF</b>                     |                             |                        |          |
| Executive functioning          | 8.8 (3.8) [1.0, 19.0]       | 10.7 (3.8) [1.0, 19.0] | 0.001    |
| Language                       | 8.7 (4.0) [1.0, 19.0]       | 11.0 (4.4) [1.0, 19.0] | <0.001   |
| Memory                         | 9.7 (4.2) [1.0, 16.0]       | 10.9 (3.8) [1.0, 16.0] | 0.028    |
| Motor skills                   | 7.5 (4.6) [1.0, 19.0]       | 10.9 (4.4) [1.0, 19.0] | <0.001   |



**Fig. 1** Scatterplot showing the relationship between cerebellar volume and five to fifteen (FTF) domain *Motor skills* in the very low birth weight (VLBW) children. The *x*-axis shows scores in the FTF and the *y*-axis shows the volume

The associations between the NEPSY II and the FTF are shown in Table 3. The NEPSY II domain *Executive functioning* was significantly associated with all the FTF domains, and the NEPSY II domain *Language* was significantly associated with the FTF domain *Language*. Furthermore, the NEPSY II domain *Memory* was significantly associated with the FTF domain *Language*, and the NEPSY II domain *Motor skills* was significantly associated with the FTF domains *Executive functioning*, *Motor skills*

and *Language*. The analyses between the NEPSY II and the FTF were repeated entering the same background variables as in the volumetric analyses. The results did not change; the significant associations remained significant and none of the non-significant associations became significant.

For the FTF, the sensitivity, i.e. how many of those who scored below normal in NEPSY II also scored below normal in FTF, and specificity, i.e., how many of those who received normal scores in NEPSY II received normal scores in FTF, were analysed. In the domain *Executive functioning*, sensitivity and specificity was 60 and 78%, respectively, and in the domain *Language*, sensitivity and specificity was 50 and 83%, respectively. In the domain *Memory*, sensitivity and specificity was 41 and 81%, respectively, and in the domain *Motor skills*, sensitivity and specificity was 58 and 60%, respectively.

## Discussion

To our knowledge, the relationship between brain volumes at term equivalent age and long-term developmental outcome has not been studied earlier in VLBW children. We found no significant associations between the brain volumes and neuropsychological functioning when neuropsychological functions were examined with neuropsychological tests. However, when neuropsychological functioning was assessed with the parental questionnaire, tapping child's performance in every day life, significant associations were found between a smaller volume of total brain tissue and poorer executive functions, between a smaller cerebellar



**Table 3** Associations (*P* value, estimated regression coefficient, standard error) between NEPSY II and five to fifteen (FTF) in the very low birth weight (VLBW) children

|                       | FTF                   |                      |                      |                       |
|-----------------------|-----------------------|----------------------|----------------------|-----------------------|
|                       | Executive functioning | Language             | Memory               | Motor skills          |
| NEPSY II              |                       |                      |                      |                       |
| Executive functioning | 0.002 (0.183, 0.058)  | 0.000 (0.202, 0.054) | 0.006 (0.151, 0.053) | 0.004 (0.138, 0.047)  |
| Language              | 0.273 (0.067, 0.060)  | 0.007 (0.153, 0.055) | 0.360 (0.051, 0.055) | 0.568 (−0.028, 0.049) |
| Memory                | 0.148 (0.112, 0.077)  | 0.022 (0.169, 0.072) | 0.096 (0.117, 0.069) | 0.133 (0.094, 0.062)  |
| Motor skills          | 0.018 (0.194, 0.080)  | 0.002 (0.246, 0.074) | 0.106 (0.122, 0.074) | 0.001 (0.225, 0.062)  |

The present associations were controlled for background variables

volume and both poorer executive functions and motor skills, and between a larger volume of brainstem and poorer language functions. Even after adjustment for total brain tissue volume, the two significant associations between the cerebellar volume and the FTF domains remained borderline significant ( $P = 0.05$ ).

In earlier studies, associations between brain volumes at term equivalent age and later outcome have been analysed up to 2 years of age, and in those studies altered volumes have been shown to relate to impaired development [4, 6, 13, 22, 28, 29, 34, 42]. Connections between brain volumes and development have also been found later in childhood and adolescence [1, 3, 21, 24], but volumes have then been measured simultaneously with a developmental assessment and, hence, the predictive value of smaller or larger volumes has not been considered. There are also studies where no statistically significant associations between volumes and outcome in preterm children have been identified [15]. Brain volumes have been shown to change relative to general growth during childhood [27] and it is possible that the effect on development of altered volumes at term equivalent age also changes.

In our study, smaller volume of the cerebellum was significantly related to poorer executive and motor functions. The association between the cerebellar volume and the motor skills remained significant even after the exclusion of the two disabled children with the smallest volumes. It is apparent from earlier studies that cerebellum is also involved in cognitive functioning in addition to motor control. In 8-year-old prematurely born children, cerebellar volume has been shown to be associated with intelligence and visuomotor functioning [23]. In adolescents born preterm, a smaller cerebellar volume has been shown to be related to lower intelligence [2], and a smaller lateral cerebellar volume to reduced executive, visuospatial, and language functions [3].

A likely reason why significant associations were found between the volumes and neuropsychological functions according to the questionnaire but not according to the tests is that, although most of the children with

neurodevelopmental impairments could be tested with the NEPSY II, some children with severe developmental impairments cannot be assessed with neuropsychological tests in a standardized manner. Consequently, the children most likely to have an abnormal brain structure were not included in the analyses between the brain volumes and the NEPSY II. In contrast, parental questionnaires can be administered regardless of developmental deficits. When we repeated the analyses of the associations between the cerebellar volumes and FTF domains and excluded the two severely handicapped children with the smallest cerebellar volumes, the association between the volume of cerebellum and executive functions was no longer significant and neither did these associations remain significant after adjustment for total brain volume.

Parents reported concerns related to their children's development that was not supported by the tests. In the domain *Executive functioning* 22%, in the *Language* domain 17%, in the *Memory* domain 19%, and in the *Motor skills* domain 40% of the children who received normal scores in the NEPSY II obtained scores below normal in the FTF. Thus, the child's behaviour and performance in everyday situations may reflect neurodevelopmental problems not revealed by psychometric tests carried out in a shielded and supporting context.

To our knowledge, there are no previous studies on the associations between the NEPSY II and the FTF. *Executive functioning* in the NEPSY II was significantly associated with all the FTF domains. This is not surprising, as attention and executive functioning are involved in tasks of memory, motor, and language skills. Memory functions in the NEPSY II were significantly related to language, but not to memory functions in FTF. This may reflect difficulties of the parents in judging whether memory functioning of a child is age appropriate or not. Functioning in the other domains may be more easily converted to everyday skills. Another possible explanation to why language skills were related to memory skills is that, two of the three subtests in the NEPSY II *Memory* domain are verbal. Furthermore, motor skills in the NEPSY II were

significantly associated with executive, motor and language functions in the FTF. It is possible that motor impairment may have affected the results of the NEPSY II subtests of the domain *Motor skills*, and the corresponding FTF domain. However, it may be assumed that the impairment is reflected similarly in both tests. NEPSY II subtests that are not intended to measure motor functions are, however, not strongly affected by motor dexterity. Predictably, language functions in the NEPSY II were associated with language functions in the FTF. The associations between the NEPSY II and the FTF were found across domains, which is likely to reflect the fact that development at 5 years of age is still relatively global rather than domain specific.

Parental questionnaires are easily administered, and consume less professional time and resources than neuropsychological examinations. However, in our study, only 41–60% of the children who had test scores below normal (standard score <8) in the psychological examination were reported to have problems in the FTF. On the other hand, of those children who were classified as normal based on the neuropsychological examination, 17–40% had difficulties according to the parents. This may reflect false positives or false negatives in either method. The parents of the VLBW children may not always perceive their children's skills objectively leading to over- or underestimation. Besides, certain problems are not easily detected in the daily activities of a preschool child. On the other hand, parents may have knowledge about child's behaviour that is not revealed in the test situation. Therefore, the FTF is a good complement to neuropsychological tests. Information about functioning in everyday situations is valuable in the planning of interventions. The questionnaire can also form a basis for the interview of the parents, as well as be useful in the feedback of the child's performance and when discussing with the parents. Through the FTF, neuropsychological difficulties become easier for a parent to comprehend. A further strength of the FTF is that it can be administered regardless of developmental impairments, as demonstrated and discussed earlier.

The FTF questionnaire has previously been proven useful in the assessment of children's development [8, 14, 19, 35]. The validity of the FTF in detecting developmental disorders in 5-year-old children has been analysed, using the earlier version of the NEPSY II, called NEPSY, as the external criterion measure [19]. The FTF domains included were significantly associated with the corresponding domains in NEPSY, and the sensitivity of the FTF was very good. The percentage of false positives was large (63%) also in that study. Apparently, the FTF is more sensitive in the screening of developmental problems in general populations than in the evaluation of neuropsychological difficulties of prematurely born children.

A limitation of this study is that some children with severe developmental impairments could not be assessed with the NEPSY II and had to be excluded from the analyses of the associations between the brain volumes and the results in the NEPSY II. A further limitation is the fact that some of the parents were not blinded for the results from the psychological assessment, which might have affected the concerns reported in the questionnaires. The FTF was sent to the parents about a month before the fifth birthday, and the psychological assessment was performed within 2 months after the birthday. Nevertheless, some of the parents had not returned the questionnaire before the psychological examination and before they received feedback of the assessment. A potential restraint is also the amount of unreturned questionnaires; the FTF was not returned by 11% of the VLBW children's families and by 20% of the control children's families. Parental education level and birth weight differed significantly between the children whose parents had returned the questionnaire and those whose parents had not done so. In earlier studies, both birth weight [12, 36] and parental education [9, 38, 39, 41] have been shown to influence developmental outcome of preterm children. In addition, the large number of statistical analyses performed in this study might have resulted in some significant associations emerging at random. It is possible that the association between a larger volume of brain stem and poorer language functions belongs to this category as its clinical relevance is not evident. Another limitation of this study is the lack of volumetric analyses for the control group, as measurement of full-term children's volumes would have enabled assessment of whether the relationship between volumes and outcome differ in preterm and full-term children. Finally, it needs to be considered that reduced brain volumes in preterm infants might be caused by some pre- and perinatal factors, for example specific disease during intensive care [7] which is not taken in account in this study.

## Conclusion

Significant associations were found between a smaller volume of total brain tissue and poorer executive functions, between a smaller cerebellar volume and both poorer executive functions and motor skills, and between a larger volume of brainstem and poorer language functions. Even after adjustment for total brain tissue volume, the two associations between the cerebellar volume and the FTF domains were at border of statistical significance. Consequently, altered brain volumes at term equivalent age appear to affect the development of VLBW children up to 5 years of age. The NEPSY II domains *Executive functioning*, *Language* and *Motor skills* were significantly

associated with the corresponding FTF domains. Overall, however, the correspondence of the NEPSY II and the FTF domain results as expressed by the sensitivity and specificity of the FTF was not very strong. This is understandable as these instruments are designed for different purposes. The NEPSY II is designed for assessment of objective performance in a controlled test situation, and as such cannot reflect all aspects of the child's skills and problems. The FTF in turn reflects parents' concerns of the child's behaviour in variable contexts. Accordingly, the instruments complement each other in the follow up of prematurely born children.

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## Appendix

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