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CLINICAL RESEARCH ARTICLE

Cerebellar volumes and language functions in school-aged children born very preterm

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BACKGROUND: Volumes of cerebellar posterior lobes have been associated with cognitive skills, such as language functioning. Children born very preterm (VPT) often have language problems. However, only total cerebellar volume has been associated with language functioning, with contradicting results. The objective of this study was to ascertain whether total cerebellar structures or specific posterior lobular structures are associated with language ability of school-aged VPT children.
METHODS: This is a prospective cohort study of 42 school-aged VPT children without major handicaps. Structural MRI was performed and the cerebellum segmentation pipeline was used for segmentation of separate lobules. Narrative retelling assessment was performed and language content and language structure scores were extracted. Linear regression analyses were used to associate language scores with whole gray matter (GM) cerebellar volume and right Crus I+II GM volume.
RESULTS: Whole cerebellar GM volume was not significantly associated with language content nor with language structure; however, right Crus I+II GM volume was significantly associated with language content ($\beta = 0.192$ (CI $= 0.033$, 0.351), $p = 0.020$).
CONCLUSIONS: GM volume of Crus I+II appears to be associated with language functions in school-aged VPT children without major handicaps, while whole cerebellar volume is not. This study showed the importance of studying cerebellar lobules separately, rather than whole cerebellar volume only, in relation to VPT children's language functions.

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IMPACT:

- GM volume of Crus I+II is associated with semantic language functions in school-aged very preterm children without overt brain injury, whereas whole cerebellar volume is not.
- This study showed the importance of studying cerebellar lobules separately, rather than whole cerebellar volume only, in relation to very preterm children's language functions.
- This study might impact future research in very preterm children. Lobular structures rather than whole cerebellar structures should be the region of interest in relation to language functions.

INTRODUCTION

Approximately 40% of children born very preterm (VPT, <32 weeks' gestation) without overt perinatal brain lesions still have language difficulties at school age,[1–6] which are most likely a consequence of atypical brain development.[7–9] Children born VPT have been shown to have smaller gray matter (GM) and white matter (WM) volumes than full term (FT) children.[9] However, the relation between language and brain structures in children born VPT is complex, as both macrostructural and microstructural brain development appear to be essential for language functioning.[7,10–13]

For a long time, the cerebellum has been relatively underexposed when it comes to relating structural brain measures to language functions in children born VPT.[14] Nevertheless, the cerebellum is among the most vulnerable structures in children born VPT as a consequence of its fast growth and rapid proliferation, migration, and maturation of progenitor cells during the third trimester of pregnancy.[15,16] Accordingly, Pieterman et al. showed that cerebellar growth impairment characterizes school-aged children born VPT without overt perinatal brain lesions.[17] Although the cerebellum was originally predominantly associated with sensorimotor skills, its involvement in cognitive processes has been highlighted more often in the past decade,[18,19] particularly in relation to the posterior lobe.[20–22] Even more specific, posterior lobule Crus I+II has been shown to be crucial in non-motor functions, such as language, and is characterized by distinct connectivity from neighboring lobules.[23]

When it comes to language functions specifically, associations have been found between cerebellar damage and atypical language functions in both children and adults.[24,25] However, without overt cerebellar damage, the relation between the

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cerebellum and language functions appears to be more subtle. In volumetric studies, a positive relationship is observed between language performances and GM volumes in the right posterior lobules in healthy, right-handed adolescents[26] and in posterior lobules in VPT children.[27] Furthermore, associations between Crus I volume and language have been found in patients with FOXP2 mutation[28] and in school-aged children with specific language impairment.[29] Besides, functional magnetic resonance imaging (fMRI) studies in healthy adults showed cerebellar activity during language tasks, predominantly in right Crus I and Crus II.[30–34] Semantic language tasks, specifically, were associated with these lobules. Also epileptic pediatric children and adolescents were shown to activate Crus I+II during a semantic decision task.[35] Since the right cerebellar hemisphere is connected with the left cerebral cortical areas that are known to support language processing, most associations with language functions have been found in the right cerebellar hemisphere.

To our knowledge, so far, six studies have investigated cerebellar volume in relation to oral language functions in children born preterm. Oral language functions reflect comprehension and production of spoken language, rather than reading or writing, or verbal fluency performance. Three of these studies showed significant positive correlations between a language test or subtest and whole cerebellar volume.[10,36,37] One study, however, did not show an association in moderate-to-late preterm children.[38] Another study did not find a relation in children born VPT but did find a relation within small for gestational age (GA) children.[39] Taken together, these studies did not show corresponding results and only one study differentiated between the cerebellar lobes.[27] However, none of these studies differentiated between cerebellar lobules, nor between the left and right cerebellar hemisphere. Nevertheless, studying the cerebellum on a more detailed, lobular level seems to be important in children born VPT, specifically in children without overt brain damage, because of their relatively good performances, but their possibly more dispersed brain network.[7,40] In addition, injured cerebellar posterior lobes have been related to impaired volumetric development of the uninjured contralateral cerebral hemisphere.[41] Predominantly, impaired growth of dorso-lateral prefrontal, premotor, and midtemporal supratentorial cortical regions have been shown in children with cerebellar damage, which was associated with poorer language performance.[24,41] These findings suggest that their specific corresponding cerebellar regions may be crucial to language functioning and development.

When assessing language functions, it is important to use a detailed approach as well. Specifically, in school-aged children, oral language functions comprise the integration of multiple language components, such as semantics (i.e., meaning of language units), syntax (i.e., structures of language units), and pragmatics (i.e., language use in context). However, most studies relating brain measures to language functions use simple, item-based language tests only, such as a vocabulary task. Stipdonk et al. recently studied complex language functions in children born VPT and found significantly lower results on both item-based language assessment and narrative retelling assessment, compared to FT controls. Narratives are not based on discrete skill testing but require integration of various linguistic skills and, therefore, represent daily, spontaneous communication more adequately.[42] Narrative ability has been described as one of the most "ecologically valid ways" in which to measure communicative competence, both in normal and clinical populations.[43,44] Besides, narrative assessment might be less mediated by attention problems than item-based tests.[45] Nevertheless, studies relating brain measures to thoroughly assessed narrative language functions are lacking in this field.

Therefore, the aim of this study is to ascertain whether cerebellar structures are crucially involved in narrative retelling ability of school-aged VPT children. More specifically, it is questioned whether total cerebellar structures or posterior lobular structures of interest (i.e., GM volume of right Crus I and Crus II) are associated with language content (i.e., semantics) or language structure (i.e., syntax) scores. Based on the literature, we hypothesized that total cerebellar volume will be associated with narrative retelling ability, but associations with lobules Crus I and Crus II will even be stronger. We also hypothesized that the association will be strongest with semantic language scores, rather than with syntactic scores.

METHOD

Participants

The present study concerns the cross-sectional data of 44 children born VPT at 10 years of age (T2). This study was part of a prospective longitudinal cohort study on speech, language, and brain development in children born VPT who had been admitted to the neonatal intensive care unit at Erasmus University Medical Centre-Sophia's Children's Hospital in Rotterdam, the Netherlands, between October 2005 and September 2008. Ethical approval has been given by the Medical Ethics Committee of Erasmus University Medical Centre (MEC-2015-591), and parents of participants have given written informed consent for participation and publication.

The study inclusion flow chart is presented in Fig. 1. Sixty-three children born at a GA between 24 and 32 weeks could be included to the longitudinal study. Exclusion criteria were: (1) severe disabilities (i.e., cerebral palsy with GMFCS level >1 or severe vision or hearing disabilities); (2) congenital abnormalities involving speech organs; (3) multiple birth; (4) primary language at home is not Dutch; and (5) overt brain injury seen on routine neuroimaging during the neonatal period, which included routine cerebral ultrasound scanning at days 1, 2, 3, and 7 and afterwards weekly ultrasound scanning until discharge. The ultrasound protocol included six coronal and five sagittal images through the anterior fontanel and mastoid fontanel scanning to detect any cerebellar lesions. Overt brain injury included: IVH grade ≥2 according to Papile,[46] post-hemorrhagic ventricular dilatation, other brain hemorrhages (including cerebellar hemorrhages), abnormal signal intensity of cortex, or deep GM and WM injury (periventricular leukomalacia grade ≥1 according to de Vries[47]). Criteria 1–4 were checked during neonatal protocol examination by the pediatrician and psychologist during neonatal period and at the age of 2 years. Severe vision disabilities were defined as very limited vision, which had to be defined by an ophthalmologist. Hearing functions were already examined at the neonatal hearing screening and were examined again within the procedure of the current study protocol, because of its crucial impact on language functioning. At age 10 years, 46 of the total 63 children were willing to participate in the MRI examination in addition to the language, cognition, and behavior assessments, during a 1-day visit to the Sophia's Children's Hospital.

The study was powered based on the primary outcome measure, the core language score of the Clinical Evaluation of Language Fundamentals-4.[48] The minimum sample size for proving a relevant difference of 8 quotient points with an SD of 20 (effect size 0.4) or a difference of 6 quotient point with an SD of 15 compared with the norm group was calculated to be 51, and 63 VPT children were included initially. The study was not powered for secondary outcomes, such as the cerebellar volumes.

Procedure

Magnetic resonance imaging. All images were acquired on a 3-Tesla scanner Discovery MR750 (General Electric, Milwaukee, WI) using an 8-channel head coil, located at Erasmus University Medical Centre-Sophia's Children's Hospital in Rotterdam. They were all acquired using the same high-resolution three-dimensional T1 inversion recovery fast spoiled gradient recalled sequence with the following parameters: echo time = 4.24 ms,

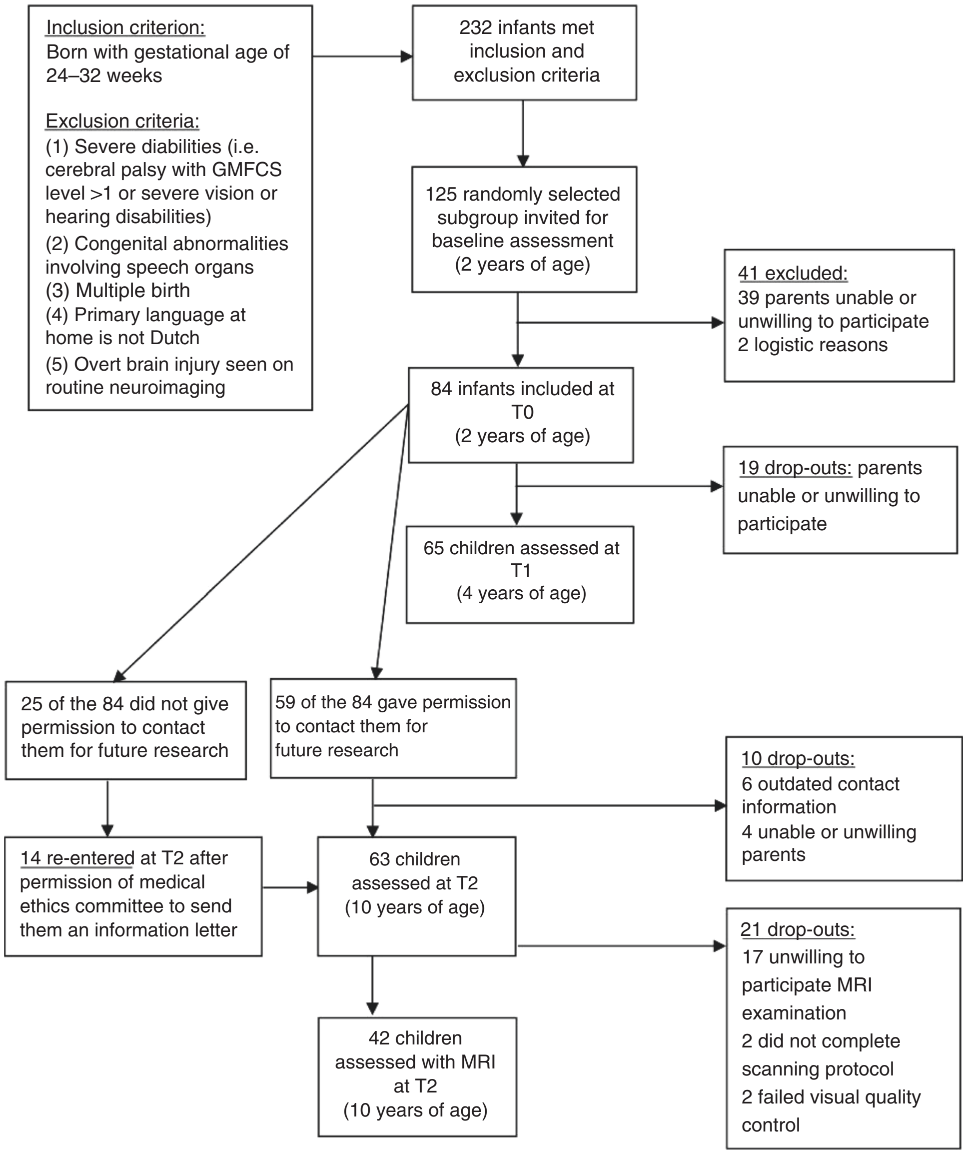

Fig. 1 Flow chart of inclusion process of the cohort. T0 = baseline time point of the study, at the age of 2. T1 = time point 1, at age 4. T2 = time point 2, at age 10. GMFCS = Gross Motor Function Classification System.

inversion time = 350 ms, repetition time = 10.26 ms, number of excitations = 1, flip angle = 16°, isotropic resolution = 0.9 mm^3. Two children did not complete the scanning protocol and their scans could not be used. Scans of 44 children were sufficient and could be used to analyze the brain morphology.

Data processing and brain morphology. Preprocessing of the T1-weighted images was twofold. First, a visual quality control was performed to check the raw images in NIfTI format for artifacts and motion, according to the procedure described by Backhausen et al.[49] Based on the degree and number of artifacts, scans were rated as "pass," "check," or "fail." A neuroradiologist who was blinded to study results assessed all MRI scans and no signs of focal brain injury (e.g., cysts or gliosis) or global brain injury (e.g., overt volume loss or abnormal signal intensities) were reported. Two images were rated as "fail" and were excluded before analysis. The scans of 42 children were sufficient and could be used for further analyses.

Second, images were preprocessed using the standard processing pipeline in FreeSurfer 6.0.[50] This pipeline included motion correction, removal of non-brain tissue (i.e., "skull stripping"), and bias field correction. The results of all scans were visually inspected for errors in the removal of non-brain tissue, artifactual deformations of the brain, and truncated brain areas.

Segmentation of the cerebellum was performed using volBrain's Cerebellum Segmentation pipeline (CERES), an online automated atlas tool.[51] After segmentation, CERES provided GM and WM volumes of the total cerebellum and the different lobules, differentiated between the right and left hemisphere. The CERES pipeline included: denoising, inhomogeneity correction, cropping, intensity normalization, and registration to the MNI125 template and subject-specific library. Total GM volume was calculated and GM volumes of the posterior lobules of interest, right Crus I and Crus II, were summed.

Linguistic assessment. Language functions were assessed by a certified speech-language pathologist during a 1-day visit to Erasmus-MC Sophia's Children's Hospital. As hearing functioning can affect oral language functions directly, hearing thresholds were measured to define possible hearing losses. Additionally, on

Table 1. Study group characteristics.

Characteristics of the study group ($n = 42$)	
Gestational age (GA) (weeks;days), mean (SD, min–max)	29;2 (1;6, 24;2 to 31;6)
Birth weight in g (BW), mean (SD, min–max)	1247 (429, 600 to 2035)
Female sex, *N* (%)	17 (41%)
Neighborhood social economic status (NSES), mean (SD)	0.08 (0.85)
Age at assessment (years;months), mean (SD, min–max)	10;5 (0;7, 9;5 to 12;0)
ADHD diagnosis, *N* (%) parent-reported	6 (14%)
Left-handed, *N* (%)	11 (25%)
Educational level mother, low to high, *N* (%)	Unknown: 4 (10%)
1: High school	1: 6 (14%)
2: Secondary vocational education	2: 15 (36%)
3: Higher vocational education	3: 14 (33%)
4: University level	4: 3 (7%)
Hearing aid one ear	1 (2%
Hearing aids both ears	2 (5%)
Received speech-language therapy in the past	21 (50%)
Language scores Renfrew's Bus story (narrative retelling assessment)	
Language Structure Score, standardized mean score (SD, CI)	−0.44 (0.87, −2.3 to 1.6)
Language Content Score, standardized mean score (SD, CI)	−0.44 (1.00, −2.5 to 1.9)
Language Structure Score <1 SD, *n* (%)	12 (29%)
Language Content Score <1 SD, *n* (%)	15 (36%)
GM volume cerebellum/cerebellar lobules	
Total cerebellum (cm^3), mean (SD)	102.4 (9.1)
Crus I+II right (cm^3), mean (SD)	20.6 (2.2)

Characteristics, mean language scores, and mean cerebellar volumes of the study group.

the assessment day the child was asked whether he/she is left or right handed.

The Renfrew Bus Story Test, validated and normed for Dutch children,[52] is an instrument of narrative retelling ability. In this story retelling assessment, integration of all language components is needed in a semi-spontaneous setting. The child's storytelling was recorded, transcribed, and coded by one of the three speech-language pathologists using Codes for the Human Analysis of Transcripts.[53] The following outcome measures were determined: information score, indicating the extent to which the child transferred the content of the story correctly; mean length of five longest utterances (ML5LU), indicating the complexity of the story and the maximum language capacity; and the number of embedded utterances (EU), indicating the complexity of the child's grammatical structures. A score for the narrative structure was calculated (in the current study referred to as "language structure"), based on ML5LU and the number of EUs. The information score was used as a measure of narrative content (in the current study referred to as "language content"). A more extensive description of the narrative retelling assessment and inter-rater reliability can be found in Stipdonk et al.[45]

Statistical analysis. Pearson's chi-square tests and independent samples *t* tests were used to compare the VPT children who participated in the present study ($n = 42$) to the non-participating VPT children of the original cohort ($n = 188$, from total $n = 232$). Differences on GA, birth weight, sex, and neighborhood social economic status (NSES) were tested. The children participating in the present study with successful scans ($n = 42$) were also compared to the children who participated at T2 but did not participate in the MRI examination ($n = 17$). Differences on GA, birth weight, sex, and NSES were tested, as well as language scores.

To study the association between cerebellar volumes and language outcome, two multiple linear regression analyses were used. In each regression model, one language measure was entered as the dependent variable (i.e., narrative structure score; narrative content score). Sex, GA, and educational level of the parents (1 = High school, 2 = Secondary vocational education, 3 = Higher vocational education, 4 = University level) were entered as confounders and whole cerebellar GM volume and right GM volume of Crus I+II as independent variables. A correlation coefficient between whole cerebellar GM volume and GM volume of right Crus I+II was calculated to check for multicollinearity, resulting in a model without whole cerebellar GM volume as well. Since left handedness is associated with atypical laterality,[54] hand preference and an interaction between hand preference and volume of right Crus I+II were included as independent variables as well in an additional model.

Adjustment for multiple testing was performed by using a Bonferroni correction. Since two *p* values (volume of Crus I+II for language content and language structure score) were relevant in the regression models, statistical significance was reached when $p < 0.025$. Statistical analyses were performed using IBM SPSS Statistics, version 25.

RESULTS

Characteristics, mean language scores, and mean volume of cerebellar lobules of the study group are presented in Table 1. Additionally, other neuropsychological (i.e., cognitive, behavioral, and language) outcomes of this study group are presented in Appendix A. The participating children ($n = 42$) did not statistically differ from the non-participating children of the initial cohort on sex, GA, and NSES, based on Pearson's chi-square tests and independent samples *t* tests. Birth weight did significantly differ, with a higher mean birth weight in the study group (1247 g) than in the non-participating group (1202 g). However, the effect size of this difference was very small (effect size $d = 0.12$). The participating children of the current study ($n = 42$) neither statistically differed from the children who participated at age 10 years but did not participate in the MRI examination on GA, birth weight, sex, educational level of the mother, age of assessment, the narrative composite, narrative structure, or narrative content score. These groups did statistically differ in NSES: the study group had significantly higher NSES (mean: 0.11, SD: 1.0) than the non-MRI group (mean: −0.52, SD: 0.9).

For the language *content* outcome, the initial multiple linear regression analysis included both total GM cerebellar volume and GM volume of Crus I+II. No significant relation with total GM cerebellar volume ($\beta = -0.018$ (confidence interval (CI) = −0.073, 0.038), $p = 0.516$) or with GM volume of right Crus I+II ($\beta = 0.248$ (CI = 0.011, 0.485), $p = 0.041$) was found after Bonferroni correction (Appendix B). The Pearson's correlation coefficient between whole cerebellar GM volume and GM volume of right Crus I+II was $r = 0.788$, which is a high correlation and may have led to multicollinearity in the linear regression model. Since whole cerebellar GM volume did not appear to be significantly associated with language content and since it might be a collider in the regression analysis for the association between Crus I+II and language content, it was removed from the final analysis (Table 2). In this analysis, the association between language content and Crus I+II GM volume was statistically significant ($\beta = 0.192$ (CI = 0.033, 0.351), $p = 0.020$) after Bonferroni correction.

Table 2. Multiple linear regression analyses.

	B	95% CI	*p* value
Dependent variable: language content			
(Constant)	−5.410	−10.904, 0.083	0.053
Right Crus I+II GM volume (in cm^3)	0.192	0.033, 0.351	0.020[a]
Gestational age (in days)	0.007	−0.021, 0.036	0.592
Sex (males)	−0.434	−1.086, 0.217	0.184
Educational level of the parent			0.905
1 = High school	−0.289	−1.660, 1.083	0.670
2 = Secondary vocational education	−0.282	−1.583, 1.019	0.661
3 = Higher vocational education	−0.069	−1.348, 1.209	0.913
4 = University level	0 (reference)		
Dependent variable: language structure			
(Constant)	−1.982	−7.334, 3.371	0.456
Right Crus I+II GM volume (in cm^3)	0.125	−0.030, 0.280	0.111
Gestational age (in days)	−0.001	−0.028, 0.026	0.947
Sex (males)	−0.043	−0.677, 0.592	0.892
Educational level of the parent			0.321
1 = High school	−1.195	−2.532, 0.141	0.078
2 = Secondary vocational education	−0.959	−2.227, 0.308	0.133
3 = Higher vocational education	−0.751	−1.997, 0.495	0.228
4 = University level	0 (reference)		

Multiple linear regression analyses with, respectively, narrative content score and narrative structure score as dependent variable and in both models right Crus I+II GM volume, gestational age (in days), sex (1 = males, 2 = females), and educational level of the parent (1 = High school, 2 = Secondary vocational education, 3 = Higher vocational education, 4 = University level) as the independent variables.
[a]Statistically significant at the Bonferroni-adjusted significance level of 0.025.

For the language *structure* outcome, the initial multiple linear regression analysis showed no significant relation with total GM cerebellar volume ($\beta = -0.005$ (CI = −0.059, 0.050), $p = 0.862$) or with GM volume of right Crus I+II ($\beta = 0.140$ (CI = −0.093, 0.372), $p = 0.230$, Appendix B). In the final analysis, without total cerebellar GM volume, the association between Crus I+II and language structure was also not significant ($\beta = 0.125$ (CI = −0.030, 0.280), $p = 0.111$, Table 2).

In additional linear regression models (Appendix B), hand preference and an interaction between hand preference and volume of right Crus I+II were included as independent variables for both the language content and language structure outcome. For language content, the combined effect of the main effect and interaction effect of handedness was not statistically significant ($F = 1.64$, $p = 0.089$). However, for language structure the associations with hand preference and interaction between hand preference and Crus I+II were statistically significant ($F = 3.49$, $p = 0.044$). The association statistically significantly differed between right- and left-handed children, showing a stronger positive association in right-handed children.

Figure 2 shows the scatter plots of the associations between volume of total GM cerebellar volume and right cerebellar posterior lobules Crus I+II with the language structure (Fig. 2a) and language content scores (Fig. 2b).

DISCUSSION

This study provides evidence that language functions of children born VPT without major handicaps may be related to lobular volumes of the cerebellum but not with total cerebellar volume. The observed association between a semi-spontaneous semantic language measure and GM volume of right lobules Crus I+II showed the importance of studying specific smaller volumes of the cerebellum, when relating cerebellar structures to complex language measures. The lack of a correlation between total cerebellar volume and a language structure or language content measure might indicate that total cerebellar volume is not associated with language problems in relatively healthy VPT children. This is in accordance with the equal cerebellar volume that was found in VPT and FT 15-year-old children, suggesting that total cerebellar volume might not be distinctive at that age.[37]

Our study results suggest that Crus I+II is important in relation to semantic language functions. The positive correlation between volume of right Crus I+II and semantic language scores is in accordance with results of fMRI studies in healthy adults[30–34] and with structural MRI studies in VPT school-aged children.[26,27] Besides, it may emphasize the previously described uniqueness of Crus I+II, (e.g., its evolutionary expansion in higher skilled primates, its unique connectivity, and longitudinal stripes compared to neighboring anterior and posterior lobules).[23] Besides, our results suggest that the relation between total cerebellar volume and oral language scores in VPT children is less important. Several studies have showed inconsistent results regarding the relation between total cerebellar volume and oral language functions.[10,36–39] These inconsistencies were possibly a consequence of the wider outcome measures that were used, for both language functions and cerebellar structures. The current study might indicate a clarification for the variability between these studies, showing a tendency of a more specific relation between semantic, semi-spontaneous language functions, and volume of right Crus I+II only.

The inclusion and exclusion criteria of the study have led to a homogeneous study group and valid results. However, the study group, therefore, may not be representative for all VPT children. Since our study group contained relatively healthy VPT children, our results might be more similar to the associations found in healthy subjects. Besides, NSES scores of the study group were significantly higher than that of the children who were unwilling to do the MRI examination at the age of 10 years. Important to note, on the other hand, is that GA, birth weight, and sex did not differ between groups, which means that biological risk factors for adverse neurocognitive outcome were representative for all VPT children. However, when less healthy VPT children or children with lower NSES would be studied, this might lead to even more evident results.

Since left handedness is associated with more bilateral brain organization[54] and 25% of the study group of the current study was left handed, an interaction between hand preference and volume of Crus I+II was added in an additional linear regression model. The association between language structure scores and Crus I+II appeared to be significant for right-handed children but not for left-handed children. However, we did not assess hand preference extensively and children might also have been mixed handed in some cases. Our results, therefore, showed importance of hand preference in relating cerebellar lobular volumes to language but they also indicate the need for further research.[55]

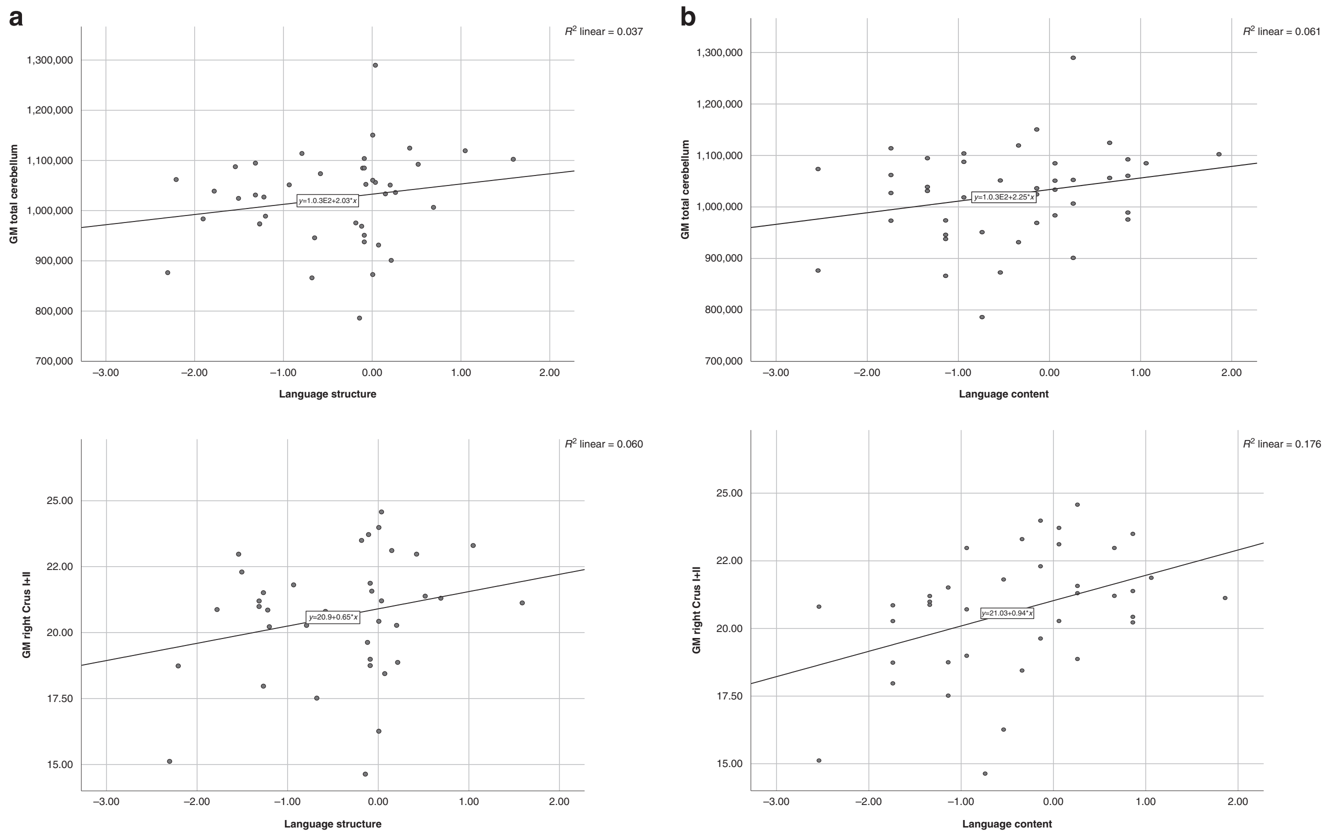

Fig. 2 Scatter plots of relations between brain measures and language measures. Total GM cerebellar volume and GM volume of right Crus I+II with narrative structure score (**a**) and narrative content score (**b**).

Strengths and limitations

The current study is unique since volumes of the cerebellar lobes and lobules were studied separately. Lobular volumes of the cerebellum have not been studied before in relation to language outcome in VPT children. Another strength of this study is that semi-spontaneous language skills of VPT children were studied in detail. In previous studies, only item-based language assessments were used, which appeal to more academic language functions rather than spontaneous language use.[6,45] Although both academic and spontaneous language use are important to the developing child, performances on item-based language tests may be impacted by the level of sustained attention of a child.[45] Since VPT children have more attention problems than FT peers,[56] narrative retelling assessment may reflect language proficiency more adequately.

A limitation of this study was the relatively small sample size ($n = 42$). As a consequence, it was not possible to statistically test all subregions of the cerebellum. Therefore, only the lobules that appeared to be regions of interest in the recent literature were tested, which had been predominantly associated with semantic language measures. Furthermore, to prevent overfitting due to the limited sample size we had to limit the number of independent variables in the models. Another limitation of this study was the lack of a control group of FT born children. Therefore, it was not possible to ascertain whether the found associations are specific to VPT children. However, the language outcomes of this study group have been compared to a control group of FT born children, which are described in another publication.[45] The VPT children's language scores were almost for all language outcome measures found to be significantly lower than that of the control group. By relating these language outcomes to cerebellar structures, the current study does add to a better understanding of the underlying brain structures of these language outcomes in VPT children. Unfortunately, MRI data were not structurally collected in the neonatal period as well. Therefore, it was not possible to study longitudinal processes, relating brain development to language development in VPT children.

Future research

For future research, it would be highly relevant to study cerebellar structures on a lobular level in relation to complex language functions in a larger sample. In addition, other language assessments, for example, item-based language tasks, might relate differently to the cerebellum. Stipdonk et al. showed that VPT children have significantly better narrative retelling skills than item-based language skills.[45] Therefore, it might be interesting to relate item-based language skills to volumes of cerebellar structures as well, using attention problem scores as a confounder variable, because of its possibly mediating role.

Besides, it would be interesting to further study the effect of hand preference on the volumetric difference between right and left cerebellar lobes and lobules. Specifically in studying language outcomes, this would gain more insight in the lateralization process in VPT children. More specifically, future research might validate whether syntactic language functions, rather than semantic language functions, are significantly affected by hand preference and right–left volumetric differences. The connection between the cerebellum and the cerebrum would also be interesting to study in more detail with tractography. It is recommended to study these cerebellar lobules in younger ages as well, since volumes of these lobules might be predictive for later language development.

CONCLUSIONS

In conclusion, specific cerebellar lobules, right Crus I+II, tended to be positively associated with semantic language functions in school-aged VPT children, whereas whole cerebellar volume was not. Syntactic language functions seem to be positively associated with GM volume of Crus I+II in right handed children only. This study showed the importance of studying cerebellar lobules separately, rather than whole cerebellar volume only, in relation to language functions in VPT children without major handicaps. Therefore, it is recommended to clinicians using neuroimaging in VPT children to study volumes of cerebellar lobules instead of studying total cerebellar volume only.

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AUTHOR CONTRIBUTIONS

We confirm that each author has met the *Pediatric Research* authorship requirements. L.W.S., M.B., K.J.P., M.-C.J.P.F., J.v.R., and J.D. have substantially contributed to conception and design, acquisition of data, or analysis and interpretation of data. All authors have drafted the article or revised it critically for important intellectual content and have given final approval of the version to be published.

ADDITIONAL INFORMATION

The online version of this article (https://doi.org/10.1038/s41390-020-01327-z) contains supplementary material, which is available to authorized users.

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