www.nature.com/pr

CLINICAL RESEARCH ARTICLE

Language lateralization in very preterm children: associating dichotic listening to interhemispheric connectivity and language performance

Lottie W. Stipdonk[1] ✉, Rianne M. Boon[2,3], Marie-Christine J. P. Franken[1], Joost van Rosmalen[4,5], André Goedegebure[1], Irwin K. Reiss[6] and Jeroen Dudink[2]

BACKGROUND: Language difficulties of very preterm (VPT) children might be related to weaker cerebral hemispheric lateralization of language. Language lateralization refers to the development of an expert region for language processing in the left hemisphere during the first years of life. Children born VPT might not develop such a dominant left hemisphere for language processing. A dichotic listening task may be a functional task to show the dominance of the left hemisphere during language processing. During this task, different acoustic events are simultaneously presented to both ears. Due to crossing fibers in the brain, right ear stimuli are transferred directly to the left hemisphere, and left ear stimuli are transferred first to the right hemisphere and then, through the corpus callosum (CC), to the left hemisphere. Dichotic listening typically shows a right ear advantage, assuming to reflect left hemispherical language dominance. The CC, in particular the splenium, is associated with auditory processing and is considered important for language lateralization. The objective of this work was to explore whether dichotic listening performance in school-aged VPT children are associated with language performance and interhemispheric connectivity.
METHODS: This is a cross-sectional study of 58 VPT children and 30 full term controls at age 10 years. Language performance and dichotic digit test (DDT) were assessed. In 44 VPT children, additionally diffusion weighted imaging (DWI) was performed using a 3 T MRI scanner. Fractional anisotropy (FA) and mean diffusivity (MD) values of the splenium of the CC were extracted.
RESULTS: Poorer right ear DDT scores were associated with poorer language performance in VPT children only ($p = 0.015$). Association between right ear DDT scores and MD of the splenium approached the level of significance ($p = 0.051$).
CONCLUSIONS: These results support the hypothesis that poor language performance in VPT children may be a consequence of weaker lateralized language organization, due to a poorly developed splenium of the CC. Dichotic listening may reflect the level of language lateralization in VPT children.

Pediatric Research (2022) 91:1841–1848; https://doi.org/10.1038/s41390-021-01671-8

IMPACT:

- Poor language performance in VPT children may be a consequence of weaker lateralized language organization, due to a poorly developed splenium of the CC.
- Dichotic listening performance may reflect the level of language lateralization in VPT children and right ear scores of a dichotic listening task are associated with both the splenium of the corpus callosum and language performance.
- If our results could be validated in future research, it suggests that poor CC development may indicate VPT children at risk for long-term language problems.

INTRODUCTION

Approximately 40% of children born very preterm (VPT, <32 weeks' gestation) experience language problems at school-age, which is alarming since language is crucial to their academic and societal achievements.[1–4] Healthy individuals are typically thought to rely on left hemispheric activity for comprehension and generation of meaningful language, specifically for processing syntactic and lexical semantic information.[5–9] Functional magnetic resonance imaging (fMRI) studies have shown dominant left hemispheric responses and right hemispheric suppression during such language tasks in full tem (FT) born infants and adults.[10,11] VPT children, on the other hand, were shown to have both hemispheres involved during

[1]Department of Otorhinolaryngology at Erasmus Medical University Centre-Sophia Children's Hospital, Rotterdam, Netherlands. [2]Division of Neonatology, Department of Pediatrics at UMCU-Wilhelmina Children's Hospital, Utrecht, Netherlands. [3]Faculty of Science at Vrije Universiteit, Amsterdam, Netherlands. [4]Department of Biostatistics, Erasmus Medical University Centre, Rotterdam, Netherlands. [5]Department of Epidemiology, Erasmus Medical University Centre, Rotterdam, Netherlands. [6]Division of Neonatology, Department of Pediatrics at Erasmus Medical University Centre-Sophia Children's Hospital, Rotterdam, Netherlands. ✉email: l.stipdonk@erasmusmc.nl

Received: 8 November 2020 Revised: 26 April 2021 Accepted: 27 April 2021
Published online: 18 August 2021

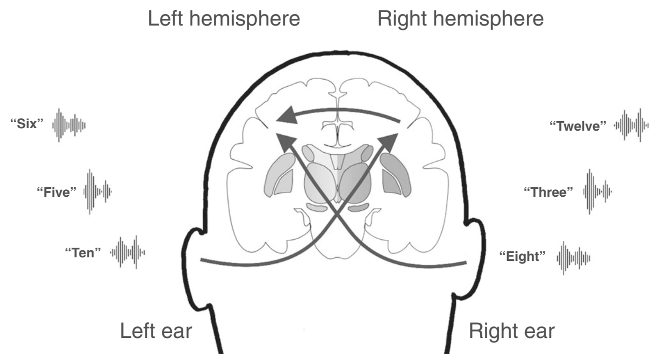

Fig. 1 Schematic figure of dichotic listening task (DDT). The arrows represent the process of left ear stimuli that are transferred to the right hemisphere and then, through the corpus callosum, to the left hemisphere. The third arrow represents the process of right ear stimuli that are transferred to the left hemisphere.

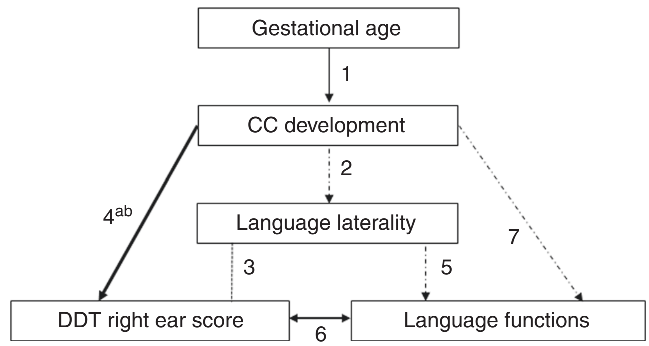

Fig. 2 Theoretical model of language lateralization in VPT children. Arrow 1 shows the relation between preterm birth and poor corpus callosum (CC) growth, already shown in previous studies. Arrow 2 shows the assumed relation between CC development and language laterality. Line 3 shows the assumed reflection of language laterality in dichotic digit test (DDT) right ear score. Arrow 4[ab] shows the relation between poor CC development and low DDT right ear score, supported by results of the current study. Arrow 5 shows the assumed relation between language laterality and language functions. Arrow 6 shows the association between DDT right ear score and language functions, found in the current study. Arrow 7 shows the assumed direct relation between DD development and language functions.

language tasks until the age of 11–12 years.[12,13] Scheinost et al. even showed a positive correlation with language functions, suggesting that better lateralization to the left hemisphere was associated with higher language scores.[14] However, contradicting results have been found regarding the associations between the level of language lateralization and language performance in VPT children.[12,13,15–18]

A cognitive complex task that relies on processing of the left and right hemisphere separately is dichotic listening. In a dichotic listening task, different acoustic events are simultaneously presented to both ears to estimate the performance of auditory segregation.[19,20] Owing to the crossing fibers between auditory nerve and cortex, right ear stimuli are transferred directly to the left hemisphere, and left ear stimuli are transferred first to the right hemisphere and then, through the corpus callosum (CC), to the left hemisphere[19] (Fig. 1). In typically developing children, a dichotic listening task shows a right ear advantage (i.e., better scores for right than left ear stimuli), which is assumed to reflect left hemispheric language dominance and thus a stronger lateralized brain organization.[19,21] Since the level of lateralization cannot be measured directly, measuring dichotic listening can be used to estimate the level of lateralization on a behavioral level. Atypical dichotic listening performance has been associated with reading problems in healthy individuals, suggesting binaural processing skills to be related to language functions.[22,23] Both stronger right ear advantage (i.e., lower left ear score and higher right ear score) as well as lower recall for both ears with weaker right ear advantage was found. A study in very low birth weight adolescents showed weaker performance of the right ear in both a free recall condition and a condition in which children were asked to focus on the right ear, but these differences were not significant.[24] However, to the knowledge of the authors, dichotic listening has never been studied in VPT school-aged children, and therefore, it is still unknown whether dichotic listening performance is associated with language performance in VPT children. Furthermore, as dichotic listening requires interhemispheric exchange *during* this task,[20] it might be associated with microstructural CC characteristics. To clarify this, Fig. 2 schematically shows the theoretical model containing hypothetical relations between dichotic listening, language performance, and interhemispheric connectivity, based on what is known from the literature.

The CC is crucial for interhemispheric communication,[25] and it has been shown that the splenium of the CC is associated with auditory processing.[26,27] This association can be explained by the commissural tracts of the temporal lobe, accommodating the auditory cortex, that run predominantly through the CC at the level of the splenium.[28,29] Besides, development of the CC during childhood is also thought to be associated with language lateralization.[30] fMRI studies in healthy individuals have shown that smaller midsagittal surface area of the CC and agenesis of the CC were associated with bilateral hemispheric activation in response to language tasks, and bigger midsagittal surface area was associated with left hemispheric activation.[31,32] VPT children were found to have altered CC development in comparison with term born children. A delay in CC growth is already detectable 6 weeks after birth in VPT infants,[33] persists throughout childhood,[34,35] and has been associated with impaired verbal skills, specifically in boys.[35] Northam et al. found significant associations between temporal interhemispheric tracts through the splenium and language ability in preterm adolescents.[36] However, the exact interaction between atypical CC development in VPT children and atypical language lateralization remains unclear. Since commissural tracts connect the auditory cortex with the splenium and dichotic listening is assumed to be associated with language lateralization, it may be a highly relevant skill to study in VPT children. Better understanding of the relations between language functions, dichotic listening, and interhemispheric connections may contribute to explaining the poor language performance of VPT children and may provide evidence for altered language organization.

Therefore, the overall aim of this study is to examine dichotic listening performance in school-aged children born VPT as an outcome measure reflecting language lateralization, relating interhemispheric connectivity to language performance (Fig. 2). Two research questions (RQs) were formulated: RQ1: Is dichotic listening performance associated with language performance in VPT and FT children? RQ2: Are fractional anisotropy (FA) and mean diffusivity (MD) values of the splenium of the CC associated with VPT children's dichotic listening performance? We hypothesized that VPT children would perform worse on dichotic listening than FT peers and that poorer dichotic listening performance would be associated with poorer language performance in VPT children. Also, we hypothesized that low FA values and high MD values of the splenium, reflecting poor interhemispheric connectivity, would be associated with poorer dichotic listening scores.

MATERIALS AND METHODS

Study population

The present study concerns the cross-sectional data of 63 VPT children at age 10 years with no evidence for severe brain injury. They were part of a

Table 1. Study sample characteristics and dichotic listening (DDT) and language scores of the VPT and FT study groups.

Characteristics	Very preterm ($n = 58$)	Very preterm subgroup with sufficient MRI ($n = 30$)	Full term ($n = 30$)	VPT group ($n = 58$) vs. VPT MRI subgroup ($n = 30$)	Total VPT group ($n = 58$) vs. FT group ($n = 30$)
Gestational age in weeks;days					
Mean (SD)	29;0 (2;1)	29;1 (2;0)	39;6 (1;3)	$p = 0.490$	$p < 0.001$
Median (interquartile range)	29;4 (27;4–30;6)	29;3 (27;3–30;5)	40;0 (39;1–41;0)		
Birth weight in g					
Mean (SD)	1195 (420)	1238 (460)	3469.1 (450)	$p = 0.404$	$p < 0.001$
Median (interquartile range)	1118 (855–1626)	1080 (840–1676)	3450 (3088–3790)		
Female sex, *N* (%)	25 (43%)	14 (45%)	11 (37%)	$p = 0.735$	$p = 0.566$
Neighborhood social economic status, mean (SD)	−0.02 (1.0)	0.10 (.92)	0.20 (.82)	$p = 0.338$	$p = 0.315$
Age (years;months) at assessment, mean (SD)	10;5 (0;8)	10;6 (0;8)	10;3 (0;11)	$p = 0.631$	$p = 0.132$
Left-handed, *N* (%)	13 (22%)	8 (25%)	1 (3%)	$p = 0.507$	$p = 0.020$
Educational level of the mother, low to high, *N* (%)	Unknown: 5 (9%)	Unknown: 3 (10%)	Unknown: 0	$p = 0.957$	$p = 0.051$
1: High school	1: 9 (16%)	1: 4 (14%)	1: 3 (10%)		
2: Secondary vocational education	2: 20 (34%)	2: 10 (33%)	2: 5 (17%)		
3: Higher vocational education	3: 18 (31%)	3: 10 (33%)	3:14 (47%)		
4: University level	4: 6 (10%)	4: 3 (10%)	4: 8 (26%)		
DDT and Language scores					
Right ear DDT % correct score (SD), min–max	64.5 (12.2), 22–85	64.8 (10.2), 37–80	70.3 (11.3), 47–92	$p = 0.839$	$p = 0.033$
Left ear DDT % correct score (SD), min–max	57.6 (12.8), 25-82	57.1 (13.1), 25–77	60.3 (12.1), 25–85	$p = 0.767$	$p = 0.332$
Core language score, *Q*-score (SD), min–max	89.4 (15.4), 55-129	90.7 (16.1), 55–129	105.1 (11.5), 78–129	$p = 0.520$	$p < 0.001$
Diffusion MRI splenium corpus callosum					
FA, mean (SD), min–max		0.85 (.04), 0.77–0.93			
MD, mean (SD), min–max		0.69 (0.06), 0.59–0.78			

Pearson's chi-square tests and independent samples *t* tests were used to compare the VPT children to the FT children and to compare the VPT subgroup of 30 VPT children to the total group of 58 VPT children on all variables.

longitudinal cohort study of language and brain development in children born VPT and 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. Children who were born with gestational age of 24–32 weeks could be included. Exclusion criteria were: (1) severe disabilities (i.e., cerebral palsy with Gross Motor Function Classification System level >1 or severe vision or hearing disabilities), (2) congenital abnormalities involving speech organs, (3) multiple births, (4) primary language at home is not Dutch. These criteria were checked during neonatal protocol examination by the pediatrician during neonatal period and by the pediatrician and a psychologist at 2 years of age. Severe vision disabilities were defined as very limited vision, as defined by an ophthalmologist. Hearing functions had been already examined at the neonatal hearing screening and were examined again within the procedure of the current study protocol, owing to its crucial impact on language functioning.

Additionally, structural MRI and diffusion weighted imaging (DWI) were performed in 44 of the 63 VPT children. The remaining 19 children, or their parents, were unwilling to participate in this additional examination or met one of the additional exclusion criteria: (1) claustrophobia, (2) non-removable non-MRI compatible implants.

Furthermore, language performance and dichotic listening were assessed in a cross-sectional control group of 30 FT born children, matched on age and sex. The same exclusion criteria as for the VPT children were applied. No MRI or DWI was performed in this group. Study characteristics of VPT and FT group are presented in Table 1.

Linguistic and hearing assessment

Language functions were assessed by a certified speech-language pathologist during a 1-day visit to the Erasmus University Medical Centre-Sophia's Children's Hospital. The Core Score of the Clinical Evaluation of Language Fundamentals-4 was used as the language outcome measure, which is normed and validated for Dutch children to detect language delays or disorders in children from 5 to 18 years of age.[37] The core language score is used to provide an overall language performance index, based on the mean of four subtests. Based on a normal distribution, the mean score for each subtest is 10 and the standard deviation (SD) is 3. For the core language score, the mean score is 100 and the SD is 15, also based on a normal distribution.

Since hearing is directly related to language functions, hearing thresholds were acquired in all participants to identify possible hearing impairments. Pure-tone audiometry and tympanometry were performed in a soundproof booth by a certified clinician, using a computer-based clinical audiometry system (Decos Technology Group, version 210.2.6 with AudioNigma interface) and TDH-39 headphones.

SPRINGER NATURE

Dichotic listening

To assess dichotic listening, the dichotic digit test (DDT) was performed using the same audiometry system. The DDT is a subtest of the Nijmeegse Test Batterij, which has been developed to detect auditory integration difficulties and which is normed for Dutch children >8.5 years of age and adults <47 years and is based on the English version by Kimura.[19,38] The DDT consists of 20 sets of 6 digits, of which 3 digits are presented in the right ear and, simultaneously, 3 in the left ear, all at 70 dB hearing level. After a set is presented to the child, (s)he is asked to repeat all digits, using a free recall concept (Fig. 1). For each ear, a proportion of correctly reported digits can be calculated. DDT performance was estimated in terms of percentage correctly reported stimuli, for the right ear and left ear separately. In 2 VPT children, hearing functions were insufficient (i.e., hearing threshold of >30 dB) and 3 other VPT children used (1 or 2) hearing aids. As the DDT has to be assessed with headphones, they could not wear their hearing aids during this test. As their hearing functions were insufficient without their hearing aids, they were excluded from the DDT analyses. Hence, 58 of the 63 participating VPT born children performed the DDT.

Image acquisition

MRI was performed on a 3 Tesla scanner Discovery MR750 (General Electric, Milwaukee, WI) using an eight-channel head coil located at the Erasmus University Medical Centre-Sophia's Children's Hospital in Rotterdam. T1 images were acquired using high-resolution three-dimensional T1 inversion recovery fast spoiled gradient recalled sequence with the following parameters: echo time = 4.24 ms, inversion time = 350 ms, repetition time = 10.26 ms, number of excitations = 1, flip angle = 16°, isotropic resolution = 0.9 mm^3. Additionally, DWI was performed using a $2.5 \times 2.5 \times 2.5$ mm^3 resolution and 256×256 mm^2 field of view. The following *B*-values were applied: B0 (10 times), B500 (9 directions), B1000 (15 directions), B1500 (23 directions), B2000 (74 directions).

Diffusion MRI data processing

Prior to processing, all scans were visually checked. Nine scans were excluded, due to (1) missing of multiple *B*-values ($n = 1$), (2) inconsistent *B*-values ($n = 1$), (3) not meeting the pre-processing requirements ($n = 1$), and (4) motion disturbance ($n = 6$). Thus, 35 scans were used for further analyses.

Processing of diffusion MRI scans was performed using the software package MRtrix3.[39] Pre-processing included Gibb's ringing artifact removal and eddy current corrections. Mean FA and MD values were directly extracted from regions of interest (ROIs) in the genu, body, and splenium of the CC (Appendix A). These ROIs were placed on a midsagittal plane and were each voxel-size 10. MD values are presented after dividing them by 1000.

Statistical analyses

Pearson's chi-square tests and independent samples *t* tests were used to compare the VPT children to the FT children and to compare the VPT subgroup of 30 VPT children to the total group of 58 VPT children on all variables.

For RQ1 (to determine whether language performance is associated with dichotic listening performance in VPT and FT children), both simple and multiple linear regression analyses were performed. First, simple linear regression analyses were performed with the core language score as the dependent variable and birth group (VPT or FT), DDT right ear, DDT left ear, DDT right–left difference, and FA and MD of the splenium of the CC as the independent variables. An interaction effect between birth group and DDT right ear score was used to check for effect modification by birth group. Second, a multiple linear regression analysis was performed with the core language score as the dependent variable and birth group, DDT right ear, DDT right–left difference, and the interaction between DDT right ear and birth group as the independent variables. Sex and educational level of the parents were entered as confounders. Third, a multiple linear regression analysis was performed with the VPT children only with the core language score as the dependent variable and DDT right ear, DDT right–left difference, birth weight, sex, and educational level as the independent variables.

For RQ2 (to examine whether DDT scores of the VPT children were associated with microstructural characteristics of the CC), two multiple linear regression analyses were performed with right ear DDT score as the dependent variable; the first with MD values of splenium of CC as the independent variable and the second with FA values of splenium of CC as the independent variable. In both models, birth weight and sex were entered as independent variables as well. Additional analyses with FA and MD values of the genu and body of the CC were done and are presented in Appendix B.

All distributions of dependent variables were checked for normality and outliers. Distributions of independent variables were also checked for outliers and, when added to a linear regression analysis, for multicollinearity. Detection of outliers for MD and FA values of the body of the CC led to removal of two data points. Similarly, one outlier data point of the genu was removed. Furthermore, all linear regression analyses were checked for linearity and homoscedasticity.

Statistical analyses were performed using IBM SPSS Statistics, version 25. Statistical significance was defined at $p < 0.05$.

RESULTS

Differences between the VPT and FT study groups were not statistically significant for age at assessment ($p = 0.132$), sex ($p = 0.566$), and neighborhood social economic status ($p = 0.315$). The difference in educational level of the mother between VP and FT children was also not significant but approached the level of significance ($p = 0.051$). Mean DDT scores, language scores, and mean FA and MD values are presented in Table 1. Also, there were no statistically significant differences between the VPT subgroup of $n = 30$ and the total VPT group of $n = 58$ (Table 1).

Regarding RQ1, a significant association between language outcome and birth group ($\beta = 15.7$ (CI = 9.2; 22.2), $p < 0.001$) was found in the simple linear regression analysis (Table 2a), which means that VPT children have worse language scores than FT children. The association between language outcome and right ear DDT score ($\beta = 0.58$ (CI = 0.32; 0.83), $p < 0.001$) was also found to be significant (Table 2a). In the multiple linear regression analysis with the VPT *and* FT children (Table 2b), there was a significant interaction effect of birth group and right ear DDT score on language outcome ($\beta = 0.65$ (CI = 0.13; 1.17), standardized $B = 1.1$, $p = 0.015$). This interaction suggests that right ear DDT score of VPT children, but not that of FT children, was significantly associated with language, even when controlled for educational level of the mother and sex. Also, in the multiple linear regression analysis with the VPT children only (Table 2c), the right DDT score showed to be significantly associated with language outcome ($\beta = 0.73$ (CI = 0.33; 1.13), $p = 0.001$). In the simple linear regression analyses (Table 2a), no significant associations were found between left ear DDT score and language outcome ($\beta = 0.19$ (CI = −0.08; 0.47), $p = 0.167$) or the difference between right ear and left ear DDT scores and language outcome ($\beta = 0.18$ (CI = −0.01; 0.38), $p = 0.069$).

With regard to RQ2, data of 30 VPT children were available for the multiple linear regression analyses (Table 3), due to the missing DDT scores in the VPT group as a result of hearing loss of these children ($n = 5$). Right ear DDT scores were significantly negatively associated with MD values of the splenium ($\beta = -71.3$ (CI = −130.1; −12.6), standardized $B = -0.4$, $p = 0.019$). However, when adjusted for sex and birth weight the association did not remain significant but still approached the level of significance ($\beta = -61.8$ (CI = −124.0; 0.04), $p = 0.051$). FA values of the splenium were not significantly associated with the right ear DDT score ($\beta = 43.2$ (CI = −42.3; 128.7), $p = 0.309$, Table 3). FA and MD values of genu and body were also not associated with the right ear DDT score (Appendix B).

DISCUSSION

The current study revealed that, in school-aged children born VPT, poorer dichotic listening skills are associated with poorer language performance *and* may be associated with decreased interhemispheric connectivity at the level of the splenium. Although the association between dichotic listening and interhemispheric

Table 2. Results of (a) simple linear regression analyses with core language score as dependent outcome variable and birth group (VPT vs. FT), right ear DDT score, left ear DDT score, right–left difference DDT score and interaction between birth group and right ear DDT score as the independent variables; (b) a multiple linear regression model with core language score as dependent outcome variable and birth group, right ear DDT score, right–left difference DDT score and the interaction between birth group and right ear DDT score as the independent variables; and (c) multiple linear regression model with core language score as dependent outcome variable for the VPT children only, with birth weight, DDT right ear, DDT right–left difference, sex, and educational level as the independent variables.

(a) Simple linear regression models (*n* = 88 (=58+30))				**(b) Multiple linear regression model (*n* = 88 (=58+30))**				**(c) Multiple linear regression model, VPT only (*n* = 58)**			
Outcome: core language score				**Outcome: core language score**				**Outcome: core language score**			
	B	**95% CI**	***p* value**		***B***	**95% CI**	***p* value**		***B***	**95% CI**	***p* value**
Birth group	15.7	9.2; 22.2	<.001**	(constant)	43.3	18.3; 68.3	0.001	(constant)	39.9	11.9; 67.8	0.006
DDT right ear	0.58	0.32; 0.83	<.001**	Birth group	55.5	19.3; 91.7	0.003**	Birth weight	0.01	−0.003; 0.02	0.193
DDT left ear	0.19	−0.08; 0.47	0.167	DDT right ear	0.18	−0.30; 0.66	0.457	DDT right ear	0.73	0.33; 1.13	0.001**
DDT right–left difference	0.18	−0.01; 0.38	0.069	DDT right–left difference	−0.10	−0.32; 0.12	0.375	DDT right–left difference	−0.04	−.33; 0.24	0.766
DDT right × birth group	−0.16	−0.26; −0.06	0.002*	DDT right × birth group	0.65	0.13; 1.17	0.015*	Sex (ref. = female)	−6.07	−13.3; 1.2	0.099
FA splenium	−15.2	−152; 121	0.822	Sex (ref. = female)	−4.6	−10.3; 1.1	0.110	Educational level of the parent			0.042*
MD splenium	−51.6	−151; 48	0.300	Educational level of the parent			0.116	Level 1 = high school	−12.06	−26.1; 2.0	0.090
				Level 1 = high school	−11.42	−21.6; −1.2	0.029	Level 2 = secondary vocational education	1.69	−10.2; 13.6	0.776
				Level 2 = secondary vocational education	−3.00	−11.7; 5.7	0.494	Level 3 = higher vocational education	2.73	−9.2; 14.7	0.647
				Level 3 = higher vocational education	−1.76	−9.9; 6.3	0.666	Level 4 = university level	0 (reference)		
				Level 4 = university level	0 (reference)						

$^{**}p < 0.005$; $^{*}p < 0.05$.

Table 3. Results of multiple regression models for the subgroup of VPT children with MRI results with right ear DDT score as dependent outcome variable and (a) MD values of the splenium of the CC and (b) FA values of the splenium as the independent variable.

(a) Multiple linear regression models of VPT subgroup (*n* = 30)				**(b) Multiple linear regression models of VPT subgroup (*n* = 30)**			
Outcome: DDT right ear score				**Outcome: DDT right ear score**			
	B	**95% CI**	***p* value**		***B***	**95% CI**	***p* value**
(constant)	101.5	54.4; 148.6	<0.001	(constant)	18.9	−55.3; 93.2	0.605
MD splenium	−61.8	−124.0; 0.04	0.051	FA splenium	43.2	−42.3; 128.7	0.309
Birth weight	0.004	−0.004; 0.012	0.290	Birth weight	0.007	−0.002; 0.015	0.112
Sex (ref. = female)	1.1	−6.0; 8.2	0.750	Sex (ref. = female)	2.0	−5.5; 9.5	0.584

In both models, adjusted for sex and birth weight.

connectivity in the analysis adjusted for sex and birth weight did not reach the level of significance ($p = 0.051$), it remains a relevant result. The studied neuronal processes comprise complex interactions of which the causality remains uncertain. However, we postulate that our results support the theoretical model presented in Fig. 2. According to this theory, VPT birth leads to poor CC development (Fig. 2, arrow 1), which has been found in previous studies.[33,34] We assume that this poor CC development may lead to poor lateralization development at a young age[35] (arrow 2). This relation is supported by the atypical and significant low right ear score on the dichotic listening test in VPT children that was found in the current study. This dichotic listening task typically shows a right ear advantage, assuming to reflect left hemispheric language dominance and may therefore closely reflect the level of lateralization of a child (line 3). In the current study, VPT children processed right ear stimuli, but not left ear stimuli, significantly worse than FT children, supporting the idea of weaker language laterality in VPT children. Furthermore, the negative association between MD of the splenium of the CC and right ear performance in VPT children (arrow 4[a]) provides some evidence that VPT children with poorer developed splenium of the CC perform worse on language tasks. This finding is in agreement with studies showing an association between the splenium of the CC and auditory processing[26,27] and with studies showing the crucial role of interhemispheric connectivity for language lateralization.[32,40] Furthermore, weaker language laterality might result in less expert regions such as a language dominant left hemisphere, which may lead to language problems in VPT children (arrow 5). This assumption is supported in the current study by the significant association between poor right ear performance and poor language performance in VPT children only (arrow 6). In the FT control group, no significant association was found. If these assumptions can be validated in future research, this might show that poor language laterality can specifically explain language problems in VPT children, but not those of FT children. However, the direction of causality of the association between poor right ear performance and language performance cannot be proven. It may also be plausible that poor language functions negatively affect the right ear performance. Furthermore, a dichotic listening task may also reflect more general auditory processing difficulties, independent of lateralization, which may impact language functions as well. Therefore, the interpretation of the current results as reflected in Fig. 2 require caution and need to be studied further in future research.

It has been suggested that early, adequate lateralization brings evolutionary advantages, especially in carrying out dual attention tasks.[41] Hence, language tasks also often require dual attention, such as listening and writing at the same time or listening and speaking in a conversation with one or more people, which are tasks that are continuously required at school and during societal communication. Less adequate lateralization might therefore negatively affect language functioning in such communicative situations specifically. Besides a poorly lateralized brain (and its consequences), poor CC development in infancy may also lead to poor interhemispheric communication in childhood and adolescence. During a dichotic listening performance, for example, CC activation is required to transfer left ear stimuli, via the right hemisphere, to the left hemisphere. A poorly developed CC might therefore also affect processing of left ear stimuli (arrow 4[b]) and language functions directly (arrow 7). However, no significant associations were found between FA and MD of the splenium and language outcome, which does not correspond with previous research showing significant associations between temporal interhemispheric tracts through the splenium and language ability in preterm adolescents.[36] Also, no associations were found between FA and MD of the splenium and left ear DDT scores.

Non-right handedness is more common among VPT children, which is also the case in our study group (22%). Although hand preference was not assessed extensively and it was not an a priori aim to study differences between right- and left-handed children, we explored this data since it may be important for future research. Our data showed that the left-handed (i.e., the non-right-handed) VPT children had a mean right–left DDT difference of −1.6 (SD 19.6), while this mean difference is 9.4 (SD 15.9) for the right-handed VPT children. Thus, non-right-handed VPT children do not have a right ear advantage. However, the non-right-handed VPT children were not excluded from the analyses, as it has been assumed that lateralization impacts handedness but it remains unknown how non-right handedness is associated with lateralization exactly.

Surprisingly, MD, but not FA, of the splenium was significantly associated with right DDT performance. Intuitively, these DWI indices are thought to be negatively associated: decreasing FA is associated with increasing MD. However, our findings suggest that the ratio between radial and axial diffusion (FA) in the splenium of the subjects remained stable, but the absolute values differed. Moreover, the absolute values appear to explain inter-individual differences on dichotic listening as only increasing MD was associated with decreasing right ear DDT scores. Increasing radial diffusivity has primarily been shown to reflect myelin damage and decreasing axial diffusivity is assumed to be indicative for axonal degeneration.[42] Accordingly, reduced myelin thickness, lower axonal density, or increased intercellular fluid in the splenium, reflecting decreased interhemispheric connectivity of the temporal projections, might have led to poorer right ear DDT scores.

Strengths and limitations

To the knowledge of the authors, this is the first study examining dichotic listening performance as an intermediate outcome measure between language performance and interhemispheric connections in VPT children. The significant associations between interhemispheric connectivity, dichotic listening, and language functions provide new insight and additional evidence for the idea of weaker language laterality in the brain of relatively healthy VPT children. Another strength is that high-angular resolution diffusion imaging (HARDI) was used with a constrained spherical deconvolution approach (i.e., optimized models that make use of diffusion MRI data with multiple *B*-values and gradient directions), which is a highly advanced in vivo method to study microstructures of neuronal tissue. HARDI data processed with MRtrix has proven to generate superior diffusion estimations compared to the commonly used concept of DTI.[43] Furthermore, the present study included MD values in addition to the more commonly used FA values only, which may reveal unique inter-individual differences.

A limitation of the study is the relatively small number of participants, especially in the subgroup of VPT children with DWI indices, and the lack of DWI indices of FT children. However, the dichotic listening performance was shown to be associated with language performance in the VPT group only. The association between dichotic listening and the DWI indices therefore appears to be specific to VPT children. Nevertheless, the FT group was a relatively homogeneous, high-performing group and did not include children with specific language impairments for example. Results of the FT controls may therefore not be generalizable to all FT children.

Future research

For future research, it would be interesting to compare the association between language lateralization and language performance of VPT children with that of FT children with specific language impairment to study whether the cause of language problems is specific to preterm birth. It is also recommended to apply fiber tracking on the separate segments of the CC. To enhance reliability and specificity of the pathological interpretations that indirectly can be drawn from diffusion measures, it would be highly recommended to obtain radial and axial diffusion measures separately. Besides, it would be interesting for future research to use a more heterogeneous group of VPT born children, since only relatively healthy VPT children were included in the current study. Other auditory processing tasks, less dependent of the language lateralization process, may also be interesting to study in VPT children to distinguish general auditory processing problems from lateralization-based processing tasks. Future research may provide guidelines for the use of dichotic listening in clinical practice as an indicator for the level of lateralization in VPT children. Given the relatively strong association between the right ear DDT score of VPT children and their language performance that was found, the not-so-time-consuming DDT might be used for monitoring the level of lateralization at multiple moments in childhood. Furthermore, it would be interesting to use fMRI to study the interhemispheric activity *during* a dichotic listening task, such as DDT in VPT children. In typically developing children, dichotic listening requires interhemispheric activity during such a task, specifically to process left ear stimuli. Therefore, it would be interesting to use fMRI to measure whether interhemispheric activity through the splenium during DDT is weaker in VPT children than in FT controls. Besides, it would be useful to study the interhemispheric connectivity with DWI also in term born children, aiming to ascertain which microstructural characteristics are specific to VPT children only. At last, lateralization remains to be a highly complicated theme in the literature of neurology of VPT children and it continues to require further research, as it may be an important indicator for long-term language problems in VPT children.

CONCLUSION

Dichotic listening performance may function as an outcome measure reflecting language lateralization, associating interhemispheric connection and language performance in VPT children. The associations between language performance, dichotic listening, and the splenium of the CC found in the current study support the hypothesis that VPT children with poor developed CC have weaker language laterality and worse language outcomes at school age than VPT children with adequate CC development and stronger language laterality. If this hypothesis could be validated in future research, it suggests that a measure of CC development at infant age may indicate VPT children at risk for long-term language problems.

REFERENCES

1. Aarnoudse-Moens, C. S. H., Weisglas-Kuperus, N., van Goudoever, J. B. & Oosterlaan, J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics* **124**, 717 (2009).
2. de Rodrigues, M. C. C., Mello, R. R. & Fonseca, S. C. Learning difficulties in schoolchildren born with very low birth weight. *J. Pediatr.* **82**, 6–14 (2006).
3. Barre, N., Morgan, A., Doyle, L. W. & Anderson, P. J. Language abilities in children who were very preterm and/or very low birth weight: a meta-analysis. *J. Pediatr.* **158**, 766.e1–774.e1 (2011).
4. van Noort-van der, Spekl. L., Franken, M. C. & Weisglas-Kuperus, N. Language functions in preterm-born children: a systematic review and meta-analysis. *Pediatrics* **129**, 745–754 (2012).
5. Natali, F. et al. Brain lateralization probed by water diffusion at the atomic to micrometric scale. *Sci. Rep.* **9**, 1–11 (2019).
6. Smits, M., Jiskoot, L. C. & Papma, J. M. White matter tracts of speech and language. *Semin. Ultrasound CT MRI* **35**, 504–516 (2014).
7. Friederici, A. D. Towards a neural basis of auditory sentence processing. *Trends Cogn. Sci.* **6**, 78–84 (2002).
8. Hagoort, P. On Broca, brain, and binding: a new framework. *Trends Cogn. Sci.* **9**, 416–423 (2005).
9. Bradshaw, A. R., Thompson, P. A., Wilson, A. C., Bishop, D. V. M. & Woodhead, Z. V. J. Measuring language lateralisation with different language tasks: a systematic review. *PeerJ* **5**, e3929 (2017).
10. Dehaene-Lambertz, G., Hertz-Pannier, L. & Dubois, J. Nature and nurture in language acquisition: anatomical and functional brain-imaging studies in infants. *Trends Neurosci.* **29**, 367–373 (2006).
11. Gotts, S. J. et al. Two distinct forms of functional lateralization in the human brain. *Proc. Natl Acad. Sci. USA* **110**, E3435 (2013).
12. Mürner-Lavanchy, I. et al. Delayed development of neural language organization in very preterm born children. *Dev. Neuropsychol.* **39**, 529–542 (2014).
13. Tseng, C.-E. J. et al. Verbal fluency is affected by altered brain lateralization in adults who were born very preterm. *eNeuro* **6**, ENEURO.0274-0218.2018 (2019).
14. Scheinost, D. et al. Cerebral lateralization is protective in the very prematurely born. *Cereb. Cortex* **25**, 1858–1866 (2015).
15. Chiarello, C., Welcome, S. E., Halderman, L. K. & Leonard, C. M. Does degree of asymmetry relate to performance? An investigation of word recognition and reading in consistent and mixed handers. *Brain Cogn.* **69**, 521–530 (2009).
16. Boles, D. B. & Barth, J. M. "Does degree of asymmetry relate to performance?" A critical review. *Brain Cogn.* **76**, 1–4 (2011).
17. Hirnstein, M., Hugdahl, K. & Hausmann, M. How brain asymmetry relates to performance – a large-scale dichotic listening study. *Front. Psychol.* **4**, 997 (2014).
18. Wilke, M., Hauser, T. K., Krägeloh-Mann, I. & Lidzba, K. Specific impairment of functional connectivity between language regions in former early preterms. *Eur. J. Paediatr. Neurol.* **17**, S23–S24 (2013).
19. Kimura, D. Functional asymmetry of the brain in dichotic listening. *Cortex* **3**, 163–178 (1967).
20. Musiek, F. E. & Weihing, J. Perspectives on dichotic listening and the corpus callosum. *Brain Cogn.* **76**, 225–232 (2011).
21. Hugdahl, K. in *Encyclopedia of Neuroscience* (ed. Squire, L. R.) 517–522 (Academic, 2009).
22. Gósy, M., Huntley Bahr, R., Gyarmathy, D. & Beke, A. Dichotic listening and sentence repetition performance in children with reading difficulties. *Clin. Linguist. Phonetics* **32**, 787–803 (2018).
23. Moncrieff, D. W. & Black, J. R. Dichotic listening deficits in children with dyslexia. *Dyslexia* **14**, 54–75 (2008).
24. Bless, J. J. et al. Cognitive control deficits in adolescents born with very low birth weight (≤ 1500 g): evidence from dichotic listening. *Scand. J. Psychol.* **54**, 179–187 (2013).
25. van der Knaap, L. J. & van der Ham, I. J. How does the corpus callosum mediate interhemispheric transfer? A review. *Behav. Brain Res.* **223**, 211–221 (2011).
26. Fabri, M., Pierpaoli, C., Barbaresi, P. & Polonara, G. Functional topography of the corpus callosum investigated by DTI and fMRI. *World J. Radiol.* **6**, 895 (2014).
27. Pollmann, S., Maertens, M., von Cramon, D. Y., Lepsien, J. & Hugdahl, K. Dichotic listening in patients with splenial and nonsplenial callosal lesions. *Neuropsychology* **16**, 56 (2002).
28. Specht, K. & Reul, J. Functional segregation of the temporal lobes into highly differentiated subsystems for auditory perception: an auditory rapid event-related fMRI-task. *Neuroimage* **20**, 1944–1954 (2003).
29. Hofer, S. & Frahm, J. Topography of the human corpus callosum revisited—comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *Neuroimage* **32**, 989–994 (2006).
30. Gazzaniga, M. S. Cerebral specialization and interhemispheric communication: does the corpus callosum enable the human condition? *Brain* **123**, 1293–1326 (2000).
31. Josse, G., Seghier, M. L., Kherif, F. & Price, C. J. Explaining function with anatomy: language lateralization and corpus callosum size. *J. Neurosci.* **28**, 14132 (2008).
32. Hinkley, L. B. N. et al. The contribution of the corpus callosum to language lateralization. *J. Neurosci.* **36**, 4522–4533 (2016).
33. Anderson, N. G., Laurent, I., Woodward, L. J. & Inder, T. E. Detection of impaired growth of the corpus callosum in premature infants. *Pediatrics* **118**, 951 (2006).
34. Allin, M. et al. Growth of the corpus callosum in adolescents born preterm. *Arch. Pediatr. Adolesc. Med.* **161**, 1183–1189 (2007).
35. Nosarti, C. et al. Corpus callosum size and very preterm birth: relationship to neuropsychological outcome. *Brain* **127**, 2080–2089 (2004).
36. Northam, G. B. et al. Interhemispheric temporal lobe connectivity predicts language impairment in adolescents born preterm. *Brain* **135**, 3781–3798 (2012).
37. Kort, W., Compaan, E. L., Schittekatte, M. & Dekker, P. H. *Clinical Evaluation of Language Fundamentals Nederlandse versie Handleiding [CELF 4, Dutch Edition, Manual]* (Pearson, 2010).
38. Neijenhuis, K. *Nijmeegse Testbatterij Auditieve Verwerkingsproblemen* (UMC St. Radboud, 2003).
39. Tournier, J. D. et al. MRtrix3: a fast, flexible and open software framework for medical image processing and visualisation. *Neuroimage* **202**, 116137 (2019).
40. Westerhausen, R. et al. The association of macro- and microstructure of the corpus callosum and language lateralisation. *Brain Lang.* **97**, 80–90 (2006).
41. Rogers, L. J., Zucca, P. & Vallortigara, G. Advantages of having a lateralized brain. *Proc. Biol. Sci.* **271**(Suppl 6), S420–S422 (2004).
42. Alexander, A. L., Lee, J. E., Lazar, M. & Field, A. S. Diffusion tensor imaging of the brain. *Neurotherapeutics* **4**, 316–329 (2007).
43. Farquharson, S. et al. White matter fiber tractography: why we need to move beyond DTI. *J. Neurosurg.* **118**, 1367–1377 (2013).

ACKNOWLEDGEMENTS

We thank all parents and children who participated in this study.

AUTHOR CONTRIBUTIONS

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

FUNDING INFORMATION

This work was supported by Dr. C.J. Vaillantfonds, Stichting Mitialto, Stichting Coolsingel under Grant number 496, and Stichting Sophia Wetenschappelijk Onderzoek under Grant number S19-24.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Parents of participants have given written informed consent for participation and publication.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41390-021-01671-8.

Correspondence and requests for materials should be addressed to L.W.S.

Reprints and permission information is available at http://www.nature.com/reprints