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Impaired language abilities and white matter abnormalities in children born very preterm and/or very low birth weight

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Abstract

Objectives—To investigate language abilities in children born very preterm (VPT; <32 weeks' gestational age (GA)) or very low birth weight (VLBW; <1500 g) at 7 years of age and compare their performances with children born at term, and to determine whether group differences could be explained by cerebral white matter abnormality on neonatal MRI.

Study design—A cohort of 198 children born <30 weeks' GA and/or <1250 g, and 70 term controls were examined. White matter abnormalities were rated quantitatively on brain MRI at term-equivalent age. Language was assessed at age 7 years using standardized language tests. Differences between groups were tested in the five language sub-domains of phonological awareness, semantics, grammar, discourse, and pragmatics. A mediation effect was tested between birth group, white matter abnormality, and language sub-domains.

Results—The VPT/VLBW group performed significantly worse than controls on all language sub-domains (all $p < .001$). White matter abnormality mediated the effect of group differences on phonological awareness, and partly mediated this effect for semantics, grammar and discourse. White matter abnormality was not significantly associated with pragmatics ($p = .13$).

Conclusions—Language is an important area of concern in children born VPT/VLBW. Neonatal white matter abnormality is an important predictor of outcome; however, different language abilities are differentially associated with neonatal white matter abnormality.

Keywords

Prematurity; development

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Children born very preterm (VPT; <32 weeks' gestational age (GA)) or very low birth weight (VLBW; <1500 g) are at an increased risk for a number of cognitive impairments in childhood.¹⁻³ Language has a crucial role in communication, academic achievement, and social function,^{4, 5} and two recent meta-analyses have demonstrated that language ability is reduced in children born VPT/VLBW compared with peers born at term.^{6, 7} In the meta-analysis by our group,⁷ language was divided into sub-domains that included semantics (the comprehension and expression of word meanings) and grammar (the form or structure of language). In these sub-domains, school-aged children born VPT/VLBW were shown to perform 0.40 to 0.59 standard deviations (SD) below term controls. However, this meta-analysis revealed that no studies had been published for other sub-domains of language, namely phonological awareness (the sounds of language), discourse (narrative in text or conversation), or pragmatics (socially and contextually appropriate use of language). In a limited number of additional studies, phonological awareness reduced in children born preterm and/or low birth weight when compared with term children.^{8, 9} It is therefore vital that language outcomes are examined comprehensively in modern cohorts of children born VPT/VLBW, using high quality methodology including the recruitment of unselected samples and a term control group.

The predominant brain pathology of prematurity is white matter abnormality, including cystic or punctate lesions, signal changes on magnetic resonance imaging (MRI), enlarged ventricles, or loss of white matter volume.¹⁰⁻¹³ A degree of white matter abnormality has been estimated to affect as many as 72% of children born VPT/VLBW.¹⁴ It has been proposed that this white matter pathology is the neural substrate for the cognitive difficulties seen in this population.^{12, 15, 16} The degree of white matter abnormality may partly account for the reduction in language ability in children born VPT/VLBW.

We hypothesised that children born VPT/VLBW would perform worse than term children, across the five language sub-domains of phonological awareness, semantics, grammar, discourse, and pragmatics. It was also predicted that white matter abnormality would partly mediate the relationship between birth group (VPT/VLBW or term) and language.

METHODS

Participants born <30 weeks' GA and/or <1250 g were prospectively recruited into the Victorian Infant Brain Study (ViBeS) cohort from the Royal Women's Hospital in Melbourne, Victoria, Australia. From July 2001 to December 2003, infants without severe congenital abnormalities were eligible for the study, and 227 who survived the neonatal period were recruited. Two children died in early childhood, leaving 225 survivors. Seventy-seven healthy control children born at term (37 to 42 weeks' GA) and of normal birth weight (>2500 g) were also recruited from the Royal Women's Hospital, Maternal and Child Health Centres, and from the community. Forty-six of the control children were recruited during the neonatal period and had an MRI scan as part of the study protocol, and 31 were recruited at age 2 years with no neonatal MRI scan. At each follow up, families were offered financial compensation for travel costs.

Children were assessed in the neonatal period, and were subsequently followed up at ages 2, 5, and 7 years. At the 7-year follow-up, 198 (88% of survivors) VPT/VLBW and 70 (91%) term children were assessed. The study was approved by the Human Research and Ethics Committees of the Royal Women's Hospital and the Royal Children's Hospital, and written consent was obtained from the parents.

At term-equivalent age, T₁ and T₂ images were acquired with a 1.5 Tesla General Electric MRI scanner. Infants were placed unsedated in a Vac Fix beanbag to reduce motion. White

matter abnormality was rated by a neurologist blind to birth group using a modified version of a rating system described previously.^{10, 14} This modified version has high intra- and inter-rater reliability, with intra-class correlation coefficients above 0.90. Six areas were rated, namely cystic lesions (score 0–4), focal signal abnormality (score 0–3), delayed myelination (score 0–2), callosal thinning (score 0–2), lateral ventricle volume (score 0–3), and white matter volume (score 0–3). The total score ranged from 0 to 17, with 0 indicating no white matter abnormality. Neonatal white matter data were collected for 191 VPT/VLBW children and 43 term children.

As part of the 2-year follow-up, parents completed a questionnaire to assess family social risk based on family structure, education of the primary caregiver, occupation of the primary income earner, employment status of the primary income earner, language spoken at home, and maternal age at birth.¹⁷ Scores ranged from 0 to 12, with high scores representing greater social disadvantage.

At the 7-year follow-up, language was assessed as part of a larger neuropsychological battery. Five sub-domains of language were assessed with a variety of standardised tests, each with acceptable test-retest reliability and content validity:^{18–20} phonological awareness was assessed with the Phonological Processing subtest of the NEPSY-II;²⁰ semantics with the Language Content Index from the Clinical Evaluation of Language Fundamentals – Fourth Edition – Australian Standardised Edition¹⁹ (CELF-4); grammar with the Language Structure Index from the CELF-4; discourse with the Making Inference subtest from the Test of Language Competence – Expanded Edition;¹⁸ and pragmatics with the Pragmatics Profile questionnaire from the CELF-4. The first four sub-domains were assessed by a trained clinician who was blinded to previous details of the children, whereas the Pragmatics Profile was completed by the parents. All test results are reported using scaled scores based on the child's age corrected for prematurity, with the exception of the Pragmatics Profile which is reported as a total raw score (as normative data are unavailable).

Children who were too impaired to perform or understand a particular test were assigned a scaled score lower than the lowest possible scaled score for the sub-domains of semantics, grammar, and discourse, to reflect a raw score of 0, and they were assigned a scaled score of 1 for the test of phonological awareness which is the equivalent of a raw score of 0 in the norms table. It was not possible to assign a score to those children whose impairment meant the Pragmatics Profile was not appropriate, because there is no scaled score equivalent. The number of children in the VPT/VLBW sample with available language data was 193 of the 198 followed up at age 7, where 5 children were excluded primarily due to incomplete assessments. All 70 term children had available language data.

Statistical analyses

Data were analyzed with Stata 12.²¹ Differences between the VPT/VLBW and term samples on neonatal and demographic variables were analyzed using simple linear regressions or Mann-Whitney U tests for continuous variables, and chi-squared analyses or Fisher's exact tests for categorical variables. Actual *p* values were reported for all analyses, with an α -level of .05.

To examine the differences between the VPT/VLBW and term samples on the five language sub-domains, a simple linear regression was conducted for each sub-domain using birth group as the predictor. These regression models were also fitted controlling for social risk score. To account for the non-independent effect of twins/triplets from the same family, robust standard errors using the Huber/White/sandwich method were used for all analyses. To examine whether group differences were due to children who were expected to have reduced language for reasons other than prematurity, analyses were repeated with the

following children excluded: those who spoke languages other than English at home (VPT/VLBW $n = 22$; term $n = 5$), had evidence of a hearing impairment from auditory brainstem response at birth or audiometry during childhood (VPT/VLBW $n = 20$; term $n = 1$), or experienced significant developmental difficulties at 7 years (i.e., Full-Scale IQ below 70 on the Wechsler Abbreviated Scale of Intelligence (WASI), and/or a diagnosis of a pervasive developmental disorder, and/or a diagnosis of severe cerebral palsy at age 7 years; VPT/VLBW $n = 17$); some children had more than one reason for exclusion. The total numbers of children remaining for this subgroup analysis were 145 VPT/VLBW and 64 term children. Proportions of language impairment were also examined, defined as those children scoring below -1.25 SD of the test mean²² (or the mean of the term sample for the Pragmatics Profile), tested using chi-squared analyses.

White matter abnormality was explored as a mediator to explain the differences between the two birth groups. To demonstrate this mediation effect, the mediator, white matter abnormality, must first significantly predict the language sub-domain of interest in a simple linear regression.^{23, 24} After this was demonstrated, hierarchical regressions were conducted, where birth group and social risk score were entered in the first step, and then white matter abnormality was entered in the second step. For white matter abnormality to explain an identified effect of birth group on a particular language sub-domain, two things would occur at the second step of the hierarchical regression:^{23, 24} the relationship between language and birth group would reduce and become non-significant, and the effect of white matter abnormality and language would be significant.

RESULTS

The mean age at assessment during the 7-year follow-up was 7.5 years (range 6.6 to 8.3) for the VPT/VLBW sample and 7.6 years (range 6.8 to 8.3) for the term sample. The perinatal and demographic characteristics of the VPT/VLBW and term samples are described in Table I. The VPT/VLBW sample differed from the term sample as expected on perinatal medical variables and proportion of singletons. The VPT/VLBW sample had higher levels of social risk, so this variable was considered in subsequent analyses. Furthermore, the children who were assessed at age 7 did not differ from those lost to follow-up on birth weight, GA, or sex, for either the term or the VPT/VLBW samples.

Group differences in language ability

On average the VPT/VLBW sample scored significantly below the term controls for all language sub-domains, and these differences remained when controlling for social risk (Table II). When removing the children who may be expected to have reduced language for other reasons (as outlined in the Methods), the mean differences between groups were slightly reduced but remained significant for all language sub-domains, both with and without controlling for social risk (Table II). The proportions of children with low language scores are presented in Table III (not adjusted for social risk).

To further examine the performances of the VPT/VLBW group, a subgroup analysis was conducted. Those born <26 weeks' did not perform significantly differently to those born 26 to 30 weeks' for any of the language sub-domains, with or without controlling for social risk (data not shown).

The contribution of white matter abnormality

White matter abnormality (the mediator variable) significantly predicted the language sub-domains of phonological awareness ($p < .001$), semantics ($p < .001$), grammar ($p < .001$), and discourse ($p < .001$), but not pragmatics ($p = .13$). Thus for pragmatics, a mediation

effect was not examined. The results from the two steps of each hierarchical regression are presented in Table IV. A mediation effect was demonstrated for phonological awareness, where the significant effect of birth group became non-significant after entering white matter abnormality. However, this was not the case for semantics, grammar, or discourse, where white matter abnormality and birth group were both significant predictors.

DISCUSSION

We assessed language abilities across five sub-domains in children born VPT/VLBW and to examine the role of white matter abnormality. Consistent with our first hypothesis, language abilities in children born VPT/VLBW at age 7 years were reduced when compared with term children, in all five of the sub-domains of language examined. This includes the range of language processing skills, so-called “lower-level” processing tasks such as phonological awareness, up to the “higher-level” language processing skills of discourse comprehension and use of language in context. The results are consistent with our meta-analysis⁷ for semantics and grammar, and with a more recent study that reported significant differences in expressive and receptive language measures between children born VPT and term controls at age 4.²⁵ The current study contributes to the literature by assessing three other important aspects of language, for which the meta-analysis identified no high quality recent studies. Our study built on previous literature, by representing a modern cohort of children born VPT/VLBW, and comparing their scores to a healthy term control group. Group differences persisted even when children with specific reasons for impairment and those who spoke a language other than English were removed, indicating that the low language scores in the VPT/VLBW sample were not simply due to other confounding factors.

Previous literature has suggested that children born VPT/VLBW exhibit a greater deficit in other cognitive areas such as executive dysfunction and visuospatial processing, with language skills relatively spared.^{26, 27} However, the current results suggest that children born VPT/VLBW also have an important deficit in language abilities which is apparent across language sub-domains. Although the mean scores for the VPT/VLBW children fell within the average range according to the test norms, the effect sizes were substantial and the proportions of VPT/VLBW children with language impairment were greater than 20%. These results highlight that language is a clinically important area of developmental concern in this population. The cognitive dysfunction in children born VPT/VLBW therefore appears to be more generalized rather than affecting specific domains of function, which is logical when considering the non-specific nature of the biological risk that these children experience.

Further investigation into the language scores of the VPT/VLBW sample revealed no differences between those born <26 weeks' GA and 26 to 30 weeks' GA, for any language sub-domain. This is consistent with results from one study of children born <36 weeks' that found no effect of gestational age after controlling for other factors.²⁸ However, it is in contrast to other literature that describes greatest risk for cognitive impairment including language associated with those born earliest and at the lowest birth weight.^{16, 29, 30} The inconsistency in the literature may be due to many reasons, including the cognitive ability examined, the age at which the child is tested, the decade in which the child was born, groups categorized by GA or birth weight, and the range of GA/birth weight examined. Further research is needed to explore this apparent lack of difference between children born at earlier and later GA in more modern cohorts.

It has been proposed that children born VPT/VLBW demonstrate impaired cognitive function compared with term children due to the presence of diffuse white matter abnormalities.^{12, 15, 16} The current study directly tested this hypothesis for the specific

cognitive function of language, which was possible with a group of term children in which a small number had low degrees of white matter abnormality on MRI. We demonstrated that neonatal white matter abnormalities were associated with performance in phonological awareness, semantics, grammar, and discourse. White matter abnormality was found to mediate the relationship between birth group and phonological awareness, indicating that this is a crucial predictive factor for this cognitive ability. However, for the other sub-domains, birth group differences remained after including white matter abnormality in the model. The associations between white matter abnormalities and different sub-domains of language have not been previously reported.

Previous research that has examined the relationship between white matter abnormality and language has used a summary language measure as the outcome. Consistent with our findings from 4 of 5 language sub-domains, Foster-Cohen et al²⁵ found that white matter abnormality was a significant predictor of overall language within their VPT sample at age 4. In contrast, other studies have reported that neonatal medical complications such as periventricular leukomalacia or severe intraventricular haemorrhage diagnosed on cranial ultrasound, are not predictive of language in children born VLBW at age 8³¹ and 16¹⁶ years. Possible explanations for these discrepancies include the age at testing, the way in which language is characterised, and poor sensitivity of the predictors, the latter acknowledged by previous authors.¹⁶ It is possible that the more sensitive measure of white matter abnormality measured on MRI more clearly reflects the mechanism by which biological risk factors influence outcome; this neonatal structural abnormality may disrupt the development of widespread language networks.

No mediation effect was found for semantics, grammar, or discourse, and pragmatics was not related to white matter abnormality. These findings suggest that prematurity factors other than white matter abnormality are contributing to the language impairments in the VPT/VLBW population. Some studies have demonstrated that other biological variables such as neonatal seizures, postnatal corticosteroids, and lung disease predict development,^{32, 33} and it is also possible that cerebral grey matter changes may independently predict language function, as this relationship has been demonstrated for other cognitive functions.³⁴ Given that family social risk differed between the birth groups, further predictors of language are also likely to be environmental in nature, potentially involving the quality of parental speech³⁵ or behavior.³⁶ It is noteworthy that in the current study, when controlling for social risk in the linear regression models with birth group, social risk was an independent significant predictor in all analyses (data not shown). Roberts et al³⁷ have proposed a cumulative model, where a range of biological, demographic, and experiential factors predict academic difficulties in children born PT/LBW. It is possible that the relative contributions of different factors may differ according to the cognitive outcome of interest, as is seen when comparing phonological awareness and pragmatics in the current study. This is consistent with the notion of specificity, where different factors in the child's development influence different aspects of language.³⁸

The proportion of term children with MRI data was 61%, and it is possible that a larger sample size may have altered the white matter analyses. An additional limitation was the use of a rating system for the neonatal MRI; other structural imaging techniques such as diffusion-weighted imaging may have been more sensitive.

In conclusion, the current study contributes to the literature of cognitive outcomes for children born VPT/VLBW by comprehensively investigating language abilities and comparing performances to term peers, and by demonstrating that this is an area of concern in the VPT/VLBW population. White matter abnormalities occurring during the neonatal period are a key predictive factor for several language abilities 7 years later. However, our

results indicate that other factors associated with prematurity are likely to also influence language ability. It is possible that environmental factors provide additional influence on language abilities; however, further research is needed to understand the most significant determinants of this important set of cognitive skills.

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ABBREVIATIONS

GA	gestational age
VLBW	very low birth weight
VPT	very preterm

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Table 1

Perinatal and demographic characteristics of the VPT/VLBW and term children.

	VPT/VLBW sample <i>n</i> [*] = 198	Term sample <i>n</i> [*] = 70	Odds ratio (95% CI)	<i>p</i>
Child characteristics				
GA (weeks), <i>M</i> (<i>SD</i>)	27.4 (1.9)	39.1 (1.3)	-	-
Birth weight (g), <i>M</i> (<i>SD</i>)	960 (222)	3322 (508)	-	-
Male sex, <i>n</i> (%)	104 (52.5)	35 (50.0)	1.1 (0.6, 2.0)	.72
Singleton, <i>n</i> (%)	114 (57.6)	66 (94.3)	0.1 (0.0, 0.2)	<.001
Perinatal medical factors				
Small for gestational age, <i>n</i> (%)	17 (8.6)	1 (2.3)	3.9 (0.6, 169.7)	.21
Apgar score at 5 mins, median (25 th and 75 th percentile)	8 (8–9)	9 (9–10)	-	<.001
Episodes of sepsis, <i>n</i> (%)	88 (44.4)	1 (2.3)	33.6 (5.4, 1373.2)	<.001
Patent ductus arteriosus, <i>n</i> (%)	99 (50.0)	0	N/A [†]	<.001
Necrotising enterocolitis, <i>n</i> (%)	21 (10.6)	0	N/A [†]	.02
Bronchopulmonary dysplasia, <i>n</i> (%)	69 (35.0)	0	N/A [†]	<.001
Length of hospital stay (days), median (25 th and 75 th percentile)	82 (68–104)	5 (4–6)	-	<.001
Antenatal corticosteroids, <i>n</i> (%)	173 (87.8)	0	N/A [†]	<.001
Postnatal corticosteroids, <i>n</i> (%)	17 (8.6)	0	N/A [†]	.04
Cystic PVL, <i>n</i> (%)	9 (4.6)	0	N/A [†]	.37
Grade III/IV IVH, <i>n</i> (%)	7 (3.6)	0	N/A [†]	1.00
White matter abnormality, median (25 th and 75 th percentile)	3 (1–4)	1 (0–2)	-	<.001
Maternal and family characteristics				
Maternal age at birth (years), <i>M</i> (<i>SD</i>)	30.4 (5.7)	31.4 (4.5)	-	.17
Social risk score, median (25 th and 75 th percentile)	2 (1–3)	1 (0–2)	-	<.001

^{*} Some sample sizes are less than the total sample due to missing data

[†] Odds ratios could not be calculated due to a 0 value in one of the cells.

GA: Gestational age; PVL: Periventricular leukomalacia; IVH: Intraventricular haemorrhage.

Table 2

Differences between the VPT/VLBW and term children for the five language sub-domains, listed first for the whole sample then for the subgroup of children.

	VPT/VLBW <i>M</i> (<i>SD</i>)	Term <i>M</i> (<i>SD</i>)	Unadjusted		Adjusted for social risk	
			Mean difference (95% CI)	<i>p</i>	Mean difference (95% CI)	<i>p</i>
Whole sample	<i>n</i> [*] = 193	<i>n</i> [*] = 70				
Phonological Awareness	9.0 (3.6)	10.9 (2.5)	-1.9 (-2.7, -1.2)	<.001	-1.6 (-2.4, -0.8)	<.001
Semantics	94.1 (19.5)	107.4 (10.6)	-13.3 (-17.1, -9.5)	<.001	-10.5 (-14.5, -6.4)	<.001
Grammar	91.3 (20.3)	106.6 (12.4)	-15.3 (-19.5, -11.2)	<.001	-12.6 (-17.1, -8.2)	<.001
Discourse	8.0 (2.7)	10.1 (2.5)	-2.1 (-2.8, -1.4)	<.001	-1.8 (-2.5, -1.0)	<.001
Pragmatics	156.5 (27.7)	173.4 (23.7)	-16.9 (-24.8, -9.0)	<.001	-14.0 (-21.8, -6.2)	<.001
Subgroup	<i>n</i> [*] = 145	<i>n</i> [*] = 64				
Phonological Awareness	9.5 (3.1)	11.0 (2.6)	-1.5 (-2.3, -0.7)	<.001	-1.2 (-2.0, -0.4)	<.01
Semantics	98.8 (14.9)	107.6 (10.8)	-8.8 (-12.6, 5.1)	<.001	-7.0 (-10.9, -3.2)	<.001
Grammar	96.2 (15.4)	106.2 (12.8)	-10.0 (-14.3, -5.8)	<.001	-8.3 (-12.5, -4.1)	<.001
Discourse	8.6 (2.6)	10.2 (2.6)	-1.6 (-2.4, -0.8)	<.001	-1.3 (-2.1, -0.6)	<.01
Pragmatics	159.8 (24.6)	173.8 (24.6)	-14.0 (-22.4, -5.6)	<.01	-12.3 (-20.5, -4.2)	<.01

* Some sample sizes are less than the total sample due to missing data.

Table 3

The proportions of children whose language scores fell below -1.25 SD of the test mean (phonological awareness, semantics, grammar, discourse) or the term sample mean (pragmatics).

	VPT $n^* = 193$	Term $n^* = 70$	Odds ratio (95% CI)	p
Phonological awareness, %	22.8	4.3	6.6 (2.0, 34.2)	.001
Semantics, %	20.3	1.4	17.6 (2.8, 722.3)	<.001
Grammar, %	23.4	2.9	10.3 (2.5, 89.3)	<.001
Discourse, %	30.1	5.7	7.1 (2.5, 27.9)	<.001
Pragmatics, %	27.8	14.6	2.3 (1.0, 6.0)	.04

*
Some sample sizes are less than the total sample due to missing data.

Hierarchical regressions exploring white matter abnormality as a mediator in the relationship between birth group and language sub-domains.

Table 4

		Birth group		White matter abnormality	
		b	n	b coefficient (95% CI)	p
Phonological Awareness	Step 1	-1.5 (-2.5, -0.5)	.003		
	2	-0.7 (-1.7, 0.4)	.19	-0.5 (-0.7, -0.2)	.001
Semantics	Step 1	-11.9 (-16.5, -7.3)	<.001		
	2	-8.1 (-13.1, -3.0)	.002	-2.2 (-3.8, -0.7)	.005
Grammar	Step 1	-12.5 (-17.6, -7.4)	<.001		
	2	-9.2 (-14.8, -3.5)	.002	-1.9 (-3.6, -0.3)	.02
Discourse	Step 1	-2.1 (-3.0, -1.2)	<.001		
	2	-1.7 (-2.7, -0.7)	.001	-0.2 (-0.4, -0.1)	.01
Pragmatics	Step 1	-16.0 (-25.1, -7.0)	.001		
	2	N/A		N/A	

Note: Both steps are controlling for social risk. N/A = not applicable.