LOTTIE STIPDONK

THE BRAINS BEHIND LANGUAGE

LANGUAGE DEVELOPMENT AND UNDERLYING NEUROLOGY IN SCHOOL-AGED CHILDREN BORN VERY PRETERM

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Lottie Willianne Stipdonk

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The Brains Behind Language

Language development and underlying neurology in school-aged children born very preterm

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Chapter 1

General Introduction

General Introduction

Language and communication are crucial for humans. The ability to produce and understand language to transmit our thoughts distinguishes humans from other species. It is even suggested that language might shape the way we think (1). Language is a complex neurological phenomenon and language problems often occur in children who were born preterm. This thesis builds a bridge between neonatology and linguistics, by revealing complex language functions in school-aged children born preterm, and relating their language performance to their structural brain development.

Epidemiology

Nowadays, children born preterm (i.e. gestational age (GA) <37 weeks) represent 7% of all births in the Netherlands. Children born very preterm (VPT, i.e. GA <32 weeks), represent 1.3% of all neonates, which means more than 2000 Dutch children are born VPT, annually (2). Fortunately, technological advances and combined efforts of obstetricians and neonatologists have resulted in increased survival rates in the last decades (3, 4). The mortality rate among children with a very low birth weight (VLBW < 1500 g) was still 95% in 1960, while in 2000 it was only 5% (5). Since 2014, survival rates have been relatively stable (2). Despite the improved perinatal care, VPT/VLBW survivors remain at risk for adverse neurodevelopmental outcomes later in life. Moreover, as a result of the decreasing mortality rate, the number of VPT children with neurocognitive problems at school-age is increasing. Since the increasing number of VPT children that did not show overt brain lesions during routine neuroimaging, interest in the long-term neurocognitive outcome has also grown in the last few decades. So far, it is known that approximately 30% of VPT children in developed countries experience significant neurodevelopmental problems at school age, such as cognitive-, motor-, severe hearing- or vision impairment, depending on GA and neonatal complications (6-8). However, growing evidence shows that many more VPT survivors without such overt neurosensory disabilities experience more subtle long term problems, such as language disorders (7, 9), fine and gross motor dysfunction (10), poor academic achievement (11), problems in executive functioning and behavior (12). To better understand the atypical language development of VPT children, an overview of normal early language development of typically developing children will be presented.

Normal early language development

Language functions develop rapidly in the first years of life, with increasing complexity of language understanding and production. Therefore, early language development is crucial to language proficiency later in life. In the pre-linguistic phase (i.e, from 0-12 months) children start babbling (e.g. "mamama", "bababa") and understanding simple, short utterances (e.g. "get your coat"). The early linguistic phase starts around the age of 15 months, producing single words for objects or persons consistently (e.g. "cat", "mommy", "chair"), and using holophrases – a single word to express several meanings by changing the sound and using gestures (e.g. "ball", "ball?" "baaaaaall!!"). Not all speech sounds have already been developed at this age, negatively impacting intelligibility of speech. On average, two-year olds start using short sentences of 2-3 words in telegraphic style, which still requires a lot of effort by the listener to understand these utterances (e.g. "doggy eat", "mommy up"). They can say around 100-300 words at this stage (13). Between the age of 2,5-5 years, vocabulary expands so that they can understand approximately 3500, and produce about 3000 words (14). In addition, grammatical functioning, speech sound production and conversation skills develop rapidly: sentences gradually become longer and more complex, using embedded sentences with less frequent vocabulary, composing sentences into stories and dynamic interactions adjusted to the context (e.g. "I cannot go outside, because the umbrella grandma gave to me is gone"). By 6-7 years of age, oral language development is almost completely developed, with the exception of vocabulary, which continues to grow into adolescence. From this age, children start learning to read and write at school.

In clinical linguistics a developmental language disorder (DLD) is defined as a neurobiological developmental disorder with a genetic base, not caused by hearing problems, low non-verbal intelligence, congenital abnormalities of speech organs, evident neurological damage or a contact disorder (15). Based on validated and normed language assessments, observations and clinical judgement, language scores of more than 1 standard deviation below the mean can be considered as a DLD (16). However, it is not yet known what causes DLD exactly, so the definition is still controversial. Alternatively, a language delay, is language development that is delayed compared to peers, as a result of, for example, poor stimulation, multilingualism or temporary hearing problems(15). Difficulties with written language (e.g. with word reading, decoding and spelling) are defined as dyslexia, if inconsistent with or "unexpected" in consideration of other aspects of development, including general intellectual abilities(17, 18). In this thesis only the oral language functions of VPT children will be discussed.

To assess receptive (i.e. understanding) and expressive (i.e. productive) language functions clinically, it is common to distinguish five subdomains:

- Phonology, reflecting the organization of speech sounds
- Semantics, referring to the meaning of language units
- Morphology, referring to internal structures of words
- Syntax, referring to structures of sentences
- Pragmatics, concerning the use of language in social contexts.

Assessing children's language proficiency requires separate analyses of these subdomains, as well as the integration of these subdomains. Standardized item-based language test batteries are based on a set of subtests, each assessing different language subdomains. These test batteries provide insight into functioning of language subdomains separately, but also provide an overall language score by calculating an average. Another way to study language is by analyzing spontaneous language use, such as conversation discourse or narrative (re)telling. On the basis of these analyses, the integration of language domains and the proficiency of language fluency can be judged. Fillmore (1979) described four dimensions of language fluency:

- Talkativeness, the ability to talk at length with few pauses
- Succinctness, the ability to talk in coherent reasoned, and 'semantically dense' sentences
- Flexibility, the ability to have appropriate things to say in a wide range of contexts
- Creativity, the ability to be creative and imaginative in language use (19).

A speaker who applies these dimensions to a high degree will be judged by listeners as a pleasurable, good (public) speaker. In contrast to standardized, item-based test batteries, spontaneous language more adequately reflects language fluency. It remains unknown how VPT children perform when more complex language tasks are used to assess their language functions.

Atypical language development in VPT children

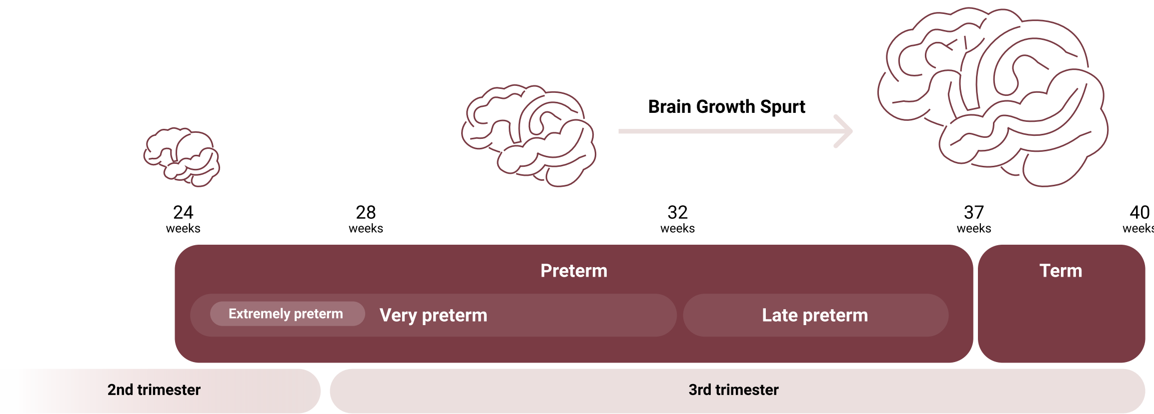
Language delays and disorders are among the most common outcomes in VPT children (20), which is alarming since language functions are crucial to academic and societal achievement and communication in everyday life. VPT children were shown to have significantly more oral language deficits than full term (FT) at both preschool and school ages (9, 21, 22). Moreover, in a systematic review and meta-analysis, Van Noort-van der Spek et al. suggest that VPT children's problems with more complex language functions increase during childhood, up to 13 years of age (9).

Children's language development, necessarily increasing in complexity during childhood, might be associated with the increasing problems with complex language functions in VPT children (9). Since language is a complex neurological phenomenon, these increasing language problems of VPT children might show a growing into deficits effect. This effect describes increasing neurodevelopmental problems throughout childhood and reflects that "early brain damage may result in a cumulative effect of ongoing development, and increasing deficits may emerge through childhood as more functions are expected to mature and will need to be subsumed within the undamaged tissues" (23).

Brain development in VPT children

Atypical language development of VPT children is often associated with atypical brain development. VPT children are born before or during the third trimester of pregnancy, a phase in which the brain grows rapidly and triples in weight. During this trimester, the delicate process of myelination occurs, which is crucial to the maturation of the brain. Myelin sheaths are wrapped around the axons enhancing the conduction efficiency along the neural network. In VPT children this brain growth spurt occurs atypically, in an extra-uterus environment (Fig 1).

Figure 1. Stages in pregnancy in human brain development.



Although the exact impact of this extra-uterine development is still unknown, magnetic resonance imaging (MRI) studies have shown several macrostructural and microstructural deviations in VPT children's brain development. These maturational deviations are obvious in VPT children with overt brain damage (24). However, VPT children without overt perinatal brain damage also show less obvious atypical brain development. In a meta-analysis of case-control studies, VPT and very low birth weight (VLBW) children without congenital anomalies were found to have significantly smaller total brain volume, smaller white and grey matter volume, smaller hippocampus, smaller corpus callosum and smaller cerebellar volume than FT controls at term equivalent age (25). Furthermore, many structural and functional MRI (fMRI) studies comparing VPT children to FT controls, have associated specific brain regions to language functions, relationships which are systematically reviewed in chapter 3 of this thesis. However, these relations appear to be diverse, since many different brain structures and many different language skills have been examined.

The cerebellum is a particularly vulnerable structure in VPT children, since it is one of the fastest growing brain structures in the third trimester of pregnancy. Therefore, it may be important to study cerebellar volumes in VPT children in more detail. The cerebellum has been predominantly linked with sensorimotor skills(26). However, in the last few decades the cerebellum has been associated with several non-motor processes as well (27, 28). More specifically, the posterior cerebellar lobe has been found to be involved in cognitive and language skills (29-31). So far only the whole cerebellar volume of VPT children without brain damage was investigated in relation to their language functions (32-35). Besides, the results of these studies do not agree, and studies relating language functions to cerebellar microstructures (i.e. left and right lobes, and lobules) are lacking. Are there smaller cerebellar lobes or lobules that are associated with language functions in VPT children?

There are also several fMRI studies showing neuronal alterations in language organization in VPT children (36-39). While healthy individuals typically show left hemispherical language dominance (40, 41), VPT children have been reported to show altered, more bilateral, language organisation (42, 43). School-aged VPT children were shown to have both hemispheres involved during language tasks until the age of 11-12 years, whereas controls typically showed dominant left-hemispheric responses and right-hemispheric suppression during language tasks, both in infancy as well as in adulthood (38, 39).

The Corpus Callosum (CC) is crucial for interhemispheric communication and is therefore assumed to play a role in the lateralization process (44). fMRI studies in healthy individuals have showed 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 hemispherical activation (45, 46). 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 (47) and persists throughout childhood (48). However, the exact interactions between atypical CC development in VPT children and atypical language lateralization remains unclear. What evidence is required to supplement our understanding of the altered language lateralization process in VPT children?

Risk factors within VPT children and their language trajectories

Many biomedical and social risk factors have been studied, trying to explain variations in long-term neurodevelopmental outcome of VPT children (49, 50).

- Biomedical risk factors, such as extremely low GA, low BW, intraventricular hemorrhage, brain lesions and white matter abnormalities are known to increase risk for adverse neurocognitive outcome (50-56).
- Postnatal treatments, such as increased duration of invasive mechanical ventilation, surgery requiring anesthetics and treatment with corticosteroids are also strongly associated with neurodevelopmental impairment (50, 57).

- Social risk factors, such as low maternal education, low parental occupation, low maternal age at birth, and multilingualism have also been associated with neurocognitive deficits in VPT children (58). These risk factors are also known to impact neurocognitive development in typically developing children (59).
- Furthermore, male sex is an important risk factor in VPT children at preschool-ages (49, 52, 60). However, male sex might only be associated with poor cognitive outcome in the toddler period, but not anymore at school ages (50).
- Preterm children also have an increased chance (2.12) of being left- or mixed-handed compared to FT children (61). Mixed handedness in the ex-preterm population has been associated with neurocognitive deficits at school-age (62). This poor lateralization of hand preference may reflect less focused neural organization (63).

Although many risk factors have been detected for neurodevelopmental disorders, it remains unknown whether there are factors which specifically increase the risk for language disorders. Regarding language development of VPT children, several developmental trajectories have been distinguished (64). Nguyen et al. distinguished stable high, stable low, resilient, precocious, and high risk trajectories. The VPT group was 8 times more likely to have a language trajectory that represented poorer language development compared with full term controls (very preterm, 40%; full term, 6%). It has also been shown that associations between delays in different neurocognitive domains (such as language, cognition and behavior) are common and even very frequent in case of neurological damage, motor and neurosensory impairments (65-67). Nevertheless, it remains unknown how functioning in these many domains interacts exactly in VPT children without overt perinatal brain lesions. Are interactions between domains age-dependent? Is it possible and useful to distinguish separate neurocognitive profiles, based on functioning in a wide range of domains?

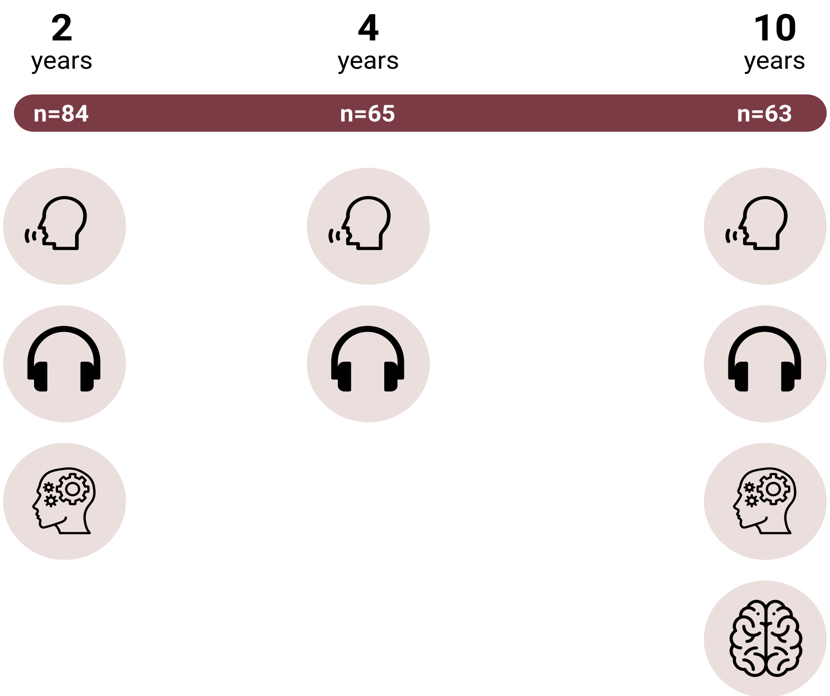
Clinical practice: Long-term follow-up of VPT children

The European Foundation for the Care of Newborn Infants (EFCNI) recently published the European Standards for Care for Newborn Health (68). They aimed to harmonize treatment and care for preterm babies across Europe by serving as a reference for the development and implementation of standards and guidelines on a national level. Most European countries have developed national multidisciplinary guidelines, prescribing a follow-up protocol of VPT and VLBW children (69, 70). According to the Dutch protocol, VPT children are followed-up at the age of 2 and in some cases also at the age of 5. The Dutch protocol also prescribes the involvement of a pediatrician-neonatologist, a physiotherapist and a psychologist, in order to achieve the early detection of developmental problems(69). These healthcare professionals assess neurological, social-emotional, mental and motor functioning of VPT children. According to the Dutch protocol, other consults can be requested, for example to assess nutrition or swallowing problems or pedagogical problems. However, follow-up assessments of the language functions of VPT children are not mentioned in these guidelines, nor is the role of a speech-language pathologist during follow-up. The EFCNI recommends the assessment of language functions at age 2. Health care specialists are recommended to attend training on standardized speech and language assessment, but a separate role for a trained and certified speech- language pathologist is currently not being addressed in the Dutch guidelines. No specific recommendations are provided for the age of language assessment. However, as it appears that complex language functions are disturbed in approximately 30% of VPT children, it may be important to assess language functions adequately during childhood. This raises important questions about the current guidelines. Are the current Dutch guidelines adapted adequately to the most recent scientific knowledge about language functions of VPT children?

Purpose of this thesis

Studying the long-term outcomes of VPT children may improve their longitudinal trajectory by offering tailor-made, evidence-based, early treatment programs. This thesis aims to ascertain the complex language functions of VPT children at 10 years of age (chapter 4 and 5) and relate these to the brain structures of these children (chapter 2, 3, 6 and 7), and their developmental trajectory from 2 to 10 years of age (chapter 8). This thesis also aims

Figure 2. Outline of longitudinal cohort study. At the age of 2 years language, hearing and cognitive and behavioral functions have been assessed in n=84 VPT children. At the age of 4 years, language and hearing functions have been assessed in n=65 VPT children. At the age of 10 years, language, hearing, cognitive and behavioral functions have been assessed in n=63 VPT children and MRI/DTI of the brain was performed in a subgroup of n=42.



to give recommendations for guidelines in clinical practice regarding language assessments, parent-counseling and treatment (Chapter 4, 5 and 8).

In 8 consecutive chapters, a multidisciplinary point of view on this topic is presented, creating unique insights regarding language development of VPT children, building bridges between scientific research and clinical practice.

Outline of this thesis

Chapter 2 and 3 present systematic reviews providing scientific background and an overview of relevant literature. In addition a meta-analysis is performed in chapter 2. **Chapters 4, 5, 6, 7 and 8** describe studies on the same longitudinally followed cohort of children, who had been admitted to the NICU at Erasmus University Medical Centre-Sophia's Children's Hospital in Rotterdam, the Netherlands, between October 2005 and September 2008. Children's language and hearing functions were assessed at the age of 2, 4 and 10 years. At the age of 2 and 10 intellectual and behavioral functioning were also measured. At the age of 10 years structural MRI and diffused tensor imaging (DTI) of the brain were performed as well (Fig 2).

More specifically, the following content will be discussed in the subsequent chapters of this thesis:

Chapter 2 investigates whether auditory neural conduction time may be an early quantitative predictive variable for developmental problems later in life. Data of 14 case-control studies which measured auditory brainstem response latencies of normal hearing infants at term equivalent age are combined in a meta-analysis. Also, the association between GA and the need for neonatal intensive care treatment with auditory conduction time is discussed.

Chapter 3 shows an overview of the extensive and diverse scientific literature on the relations between language outcome and underlying brain structures in preterm born children at school age. A systematic review of 23 studies shows the relations between oral language functions, verbal fluency and written language functions with white matter, gray matter, corpus callosum and cerebellum volume and FA of the arcuate, uncinate and superior longitudinal fasciculus.

Chapter 4 provides clinical indications for language assessments in school-age VPT children. Language functions of 63 ten-year-old VPT children without major handicaps are compared to their vocabulary knowledge, intellectual and executive functions and behavioral problems. It reveals unexpected differences between neurocognitive outcome measures and their associations, leading to recommendations for follow-up guidelines in clinical practice.

Chapter 5 presents in-depth analyses of complex language functions of VPT and FT children at school age. The case-control study shows differences between item-based language assessment and spontaneous narrative retelling assessment of VPT and FT children. What does their performances tell us about their academic and societal language use? Also, the possible mediating role of a child's level of sustained attention in different language tasks will be discussed.

Chapter 6 relates macro and microstructures of the cerebellum to language functions in school aged VPT children. Since microstructures have, so far, not been associated with language, this chapter adds to the literature about the role of the cerebellum in language functioning.

Chapter 7 presents results supporting the hypothesis that poor language performance in VPT children may be a consequence of weaker lateralized language organization, due to a poorly developed corpus callosum. It discusses the possible role of laterality in the language development of VPT children. Although language laterality is a highly complicated subject, it may be crucial to better understand the language problems of VPT children.

Chapter 8 describes the developmental trajectories of 4 different neurocognitive profiles within a group of VPT children. This chapter shows an innovative, profile-oriented method by centralizing the coherent neurocognitive outcomes of children at the age of 2 years, and longitudinally follow these profiles until the age of 10 years. The results provide indications for parent counseling and individualized intervention.

Chapter 9 concludes this thesis by describing and interpreting all findings, providing recommendations for clinical practice and suggesting ideas for future research.

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Language functions deserve more attention in follow-up of

Language and brain structures in preterm children: A systematic review

Neurodevelopmental profiles preterms

Auditory maturation preterm

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

Lateralization in very preterm children

Narrative retelling in preterm born children.

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brain

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Chapter 2

Auditory brainstem maturation in normal-hearing preterm infants: A meta-analysis

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ABSTRACT

Aim

Children born preterm often have neurodevelopmental problems later in life. Abnormal maturation of the auditory brainstem in the presence of normal hearing might be a marker for these problems. We conducted a meta-analysis of auditory brainstem response (ABR) latencies at term age to describe differences in auditory brainstem maturation between normal-hearing preterm and term-born infants.

Method

Computerized databases were searched for studies published between 1995 and 2014 that reported ABR measurements at term age in infants born preterm in a case–control design. Five peaks reflect the conduction of a neural signal along the brainstem auditory pathway. We collected I to V interpeak latency data, and III to V interpeak latency data, which refers to the more central part of the pathway.

Results

Preterm-born infants' III to V interval is significantly longer compared to infants born at term (0.081ms, effect-size=0.974), which also reflects on the I to V interval. Moreover, significantly increased ABR interpeak latencies of infants born preterm are related to lower gestational age and the need for neonatal intensive care treatment.

Interpretation

The delayed conduction time towards and into the auditory brainstem at term age suggests atypical maturation of the brainstem in normal-hearing infants born preterm. Both the duration of gestation and the consequences of the preterm birth (intensive care needed) negatively affect maturation of the auditory brainstem, which may influence later development.

Introduction

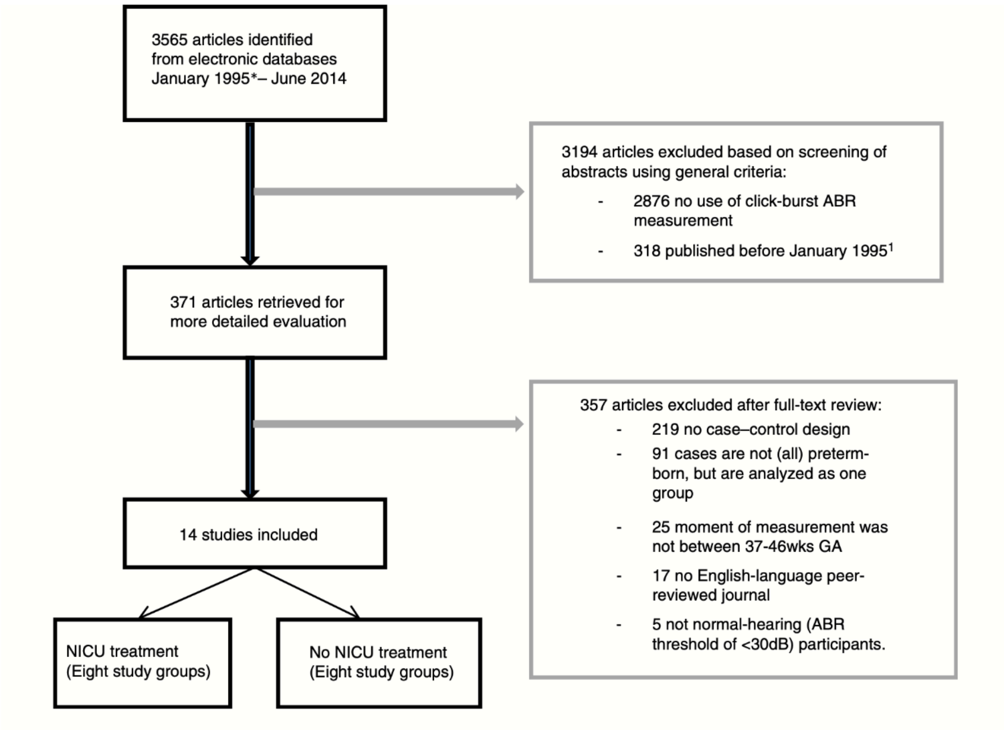
Since 1995 the survival rates for infants born preterm have risen, a consequence of technological advances and the efforts of obstetricians and neonatologists (1). Moderate and severe disabilities are detected in 8% to 14% of very preterm children (2); an even higher percentage of children born preterm have learning and behavioural problems at school age, however, such as neurocognitive problems, lower IQ, delayed motor skills, and language and speech delays (3–7). Early detection of maturation abnormalities is necessary to predict neurodevelopmental problems later in life (8,9), but only a few objective, functional, early proxy biomarkers of future neurodevelopmental outcome in newborn infants are available. It has been suggested that the auditory neural conduction time may be useful as an early quantitative predictive variable for developmental problems later in life, because it can be accurately monitored at term age and is an important marker for brainstem maturation.8,9

The third trimester of pregnancy – i.e. from 25 weeks gestational age – is highly important for the maturation of the auditory neural system. Myelination of the cochlear nerve between the cochlea and the brainstem begins, which leads to a rapid synchronized conduction along the nerve (10,11). Because infants born preterm are born in the third trimester of pregnancy, the delicate process of myelination occurs in an extra-uterine environment. It is unclear whether this early extra-uterine exposure accelerates or delays the neural auditory maturation. Lower gestational age (GA) has been associated, however, with an increased incidence of neurodevelopmental abnormalities (12).

The early third trimester is marked by the fetus' first behavioural and physiological responses to sound,10 and by recordable auditory brainstem responses (ABR). ABR parameters are sensitive to maturation of the auditory nerve and brainstem (13–16), and therefore are an adequate tool to monitor auditory brainstem maturation. The auditory system can be measured from the cochlea (periphery) through the auditory nerve into the brainstem. Five peaks reflect the conduction of a neural signal as a result of a sound stimulus along the auditory nerve and different levels of the brainstem. The interval from peak one to five (I–V) can be separated into a peripheral (I–III) and central region (III–V). Some studies have shown that various unfavourable perinatal conditions can damage an immature brainstem (12,17). Some studies have reported delayed ABR in infants born preterm (11,18,19). However, other studies found no differences between preterm- and term-born infants (20,21).

To identify possible differences in auditory conduction time, reflected by ABR interpeak latency intervals between normal-hearing preterm- and term-born infants at term age, we conducted a meta-analysis of relevant published studies. Because individual study results are equivocal (11,18–21), this meta-analysis could be of great value for this field of interest. A secondary aim was assessment of the effect of GA, as well as the effect of the need for intensive care treatment in the neonatal period on the conduction time. We hypothesized that infants born preterm have a delayed auditory conduction time, primarily arising in the central region, i.e. the brainstem area. Furthermore, it was hypothesized that lower GA and the need for neonatal intensive care treatment affects the conduction time negatively and leads to longer conduction times.

Figure 1. Flow diagram for selection of articles.



* 1995 was chosen because it signalled significant improvements in neonatal care resulting in a much better condition of infants born preterm from that time on. ABR: auditory brainstem responses; NICU: neonatal intensive care unit; GA: gestational age.

Method

Selection of studies

Relevant articles were collected by first searching the Embase, Medline OvidSP, Web-of-Knowledge, Cochrane, PubMed, and Google Scholar databases using the search terms: prematur*, preterm*, low birth weight*, intrauterine AND auditor*, hearing, deaf, and audiometr* (asterisks denote that other words including these terms are also included, e.g. ‘prematurity’ or ‘premature’). Only articles from 1995 and until June 2014 – to account for the great improvements in the care for infants born preterm from that period onwards – were viewed. The search strategy yielded 6247 citations. After duplicates were removed, 3565 records remained. The further selection process and the exclusion criteria are presented in Figure 1.

Population and data extraction

Fourteen studies meeting our search terms and exclusion criteria could be included in the meta-analysis. In all included studies, cases were matched to term-born (GA>37wks) healthy controls, born and measured in the same hospital as cases. Note that in the cases and controls of all studies, ABR thresholds were <30dB, to avoid any influence of significant peripheral hearing abnormality on measurement of ABR components. We refer to these cases and controls as normal-hearing participants, although with thresholds of <30dB some mild hearing losses cannot be excluded completely. The majority of studies reported data of neonatal complications, but did not include this as a factor in the statistical analysis. Most studies did not provide antenatal and/or perinatal factors and/or information about the severity of the complications or the length of the neonatal intensive care unit (NICU) stay. Therefore, we decided to only analyze differences between study groups with and study groups without complications. Two studies (nos. 4 and 7) reported data of two study groups – with and without the need for NICU treatment – next to their control group. We divided these studies into two separate sub-studies, which allowed us to apply a more sophisticated analysis of the impact of NICU treatment on the main ABR outcome measures (the result was no different when studies 4a and b, and 7a and b, were excluded from the analysis).

As a result, the meta-analysis concerned 16 study groups, eight including children receiving NICU treatment and eight including children not receiving NICU treatment. The meta-analysis sample comprised a total of 709 preterm-born infants and 468 term-born infants. In all 16 study groups, click-burst ABR was measured with one or more click rates. We included data of the lowest click rate with a maximum of 100/second. In 12 of the 14 studies, the left ear was measured. In two studies (nos. 5 and 10) only the mean scores of both ears were given. In some studies the results were presented solely as graphics. To obtain the numerical data we used the Java program PlotDigitizer (Free Software Foundation, Boston, MA, USA), which determined the numerical data in milliseconds to five decimal places. The main characteristics per study group are presented in Table I.

Quality assessment

Two authors (LS and AG) independently assessed the methodological quality of the included studies according to the Newcastle–Ottawa Scale.36 This scale assesses the quality of case–control design studies in terms of the selection of the population, the comparability of the study groups, and the outcome assessment. The total rating score ranges from 1 to 9 stars, with 9 being the most favourable. Any disagreement between the two assessors with regard to the total score was resolved by discussion. The 14 included studies were very similar in their study design with a structured method description. Quality of the studies was scored with either 7 or 8 stars.

Outcome measures

The ABR interval between peaks III and V, as a subcomponent of the I to V interval, served as the main outcome measure in our meta-analysis, because it is often mentioned in ABR literature as a measure of neural activity towards the auditory brainstem in newborn infants. I to III interval data could not be analyzed because they were hardly reported.

Secondary outcome measures were the separate latencies of peak I and peak V. Peak I reflects the neural activity in the auditory nerve. Peak V reflects the activity from the lateral lemniscus towards the inferior colliculus in the brainstem. However, not all included studies presented data for peaks I and V (Table 1).

Statistical analysis

We modelled the ABR differences (ΔABR) between groups via a linear random effects meta-regression as follows: where β1, β2, and β3, are corresponding parameters for intercept, the effect of the need of NICU treatment, and the effect of GA respectively. b_i are the random effects, which capture the heterogeneity between the studies in the model. ε_i and b_i are assumed mutually independent and normally distributed with different variances, i.e. $\varepsilon_i \sim N(0,\sigma_\varepsilon)$ and $b_i \sim N(0, \sigma^2_b)$. We used the maximum of GA to represent GA because it was the only available variable for all studies. Maximum GA correlates fairly well with the average GA for the studies in which both parameters were available (R=0.73, p<0.01). Results are reported as estimated parameters with 95% confidence intervals (CI). All statistical models were conducted in Bayesian statistics. All statistical analyses were performed by the Stan interface in R (NumFocus, Austin, TX, USA).

$$\Delta\mathrm{ABR}_i = \beta_1 + b_i + \beta_2 \times \mathrm{NICU}_i + \beta_3 \times \mathrm{GA}_i + \varepsilon_i$$
$$i = 1, 2, 3, \ldots, 16$$

Results

Preterm-born infants' III to V intervals are significantly longer than those of term-born infants in ABR measurement (ΔABR=0.081ms, 95% CI=0.055–0.110ms, p<0.001; Q-statistics=86.78, p<0.001, I^2=82.7% [73.1%; 88.9%]). The effect size of this mean difference was large (Hedges' g=0.974). Correspondingly, the I to V interval was also

Table 1. Characteristics of studies included in the Meta-analysis.

Study number, Author (y)	n study group (preterm)	n control group (term)	GA study group (mean, SD, min–max)	NICU treatment	Click rate ABR (per seconds)	Quality Assessment Score	Outcome measures ABR
1. Jiang et al. (2001)[22]	70	22	28.7 (2.9) 24–35	Yes	21	8	I, V, I–V, and III-V
2. Jiang et al. (2004)[23]	30	36	33.6 (2.4) 31–36	No	21	8	I, V, I–V, and III-V
3. Jiang et al. (2011)[24]	52	37	34.4 (1.8) 33–36	Yes	21	7	I, V, I–V, and III-V
4.Jiang et al. (2005)[25]	110	38	32.6 (2.1) 30–36	Two groups	Unknown	7	I, V, I–V, and III-V
5. Kilic et al. (2007)[26]	29	29	32.6 (3.3) <37	Yes	11	7	I, V, I–V, and III-V
6. Valkama et al. (2001)[27]	51	21	29.3 (2.2) <34	Yes	91	8	I, V, I–V, and III-V
7. Jiang et al. (2012)[28]	103	76	34.3 (1.6) 33–36	Two groups	21	7	I, V, I–V, and III-V
8. Jiang and Wilkinson (2008)[29]	39	37	33–36	No	91	7	I, V, I–V, and III-V
9. Li et al. (2011)[30]	31	35	34.3 (1.1) 33–36	No	31.3	7	I, V, I–V, and III-V
10. Li et al. (2013)[31]	111	92	27–36	No	91	8	I, V, I–V, and III-V
11. Jiang (2013)[32]	163	49	34.6 (1.1) 33–36	Yes	21	7	I–V, and III-V
12. Jiang et al. (2002)[33]	62	42	28.0 (2.2) 24–32	Yes	91	8	I, V, I–V, and III-V
13. Jiang et al. (2006)[34]	30	38	30.8 (0.7) 30–32	No	21	7	V, I–V, and III-V
14. Jiang et al. (2009)[35]	174	56	32.3 (2.1) 30–35	No	21	7	I–V, and III-V

GA: gestational age; NICU: neonatal intensive care unit; ABR: auditory brainstem responses.

significantly delayed in infants born preterm compared to term-born infants (ΔABR=0.073ms, 95% CI=0.036–0.122 ms, p<0.001; Q-statistics=87.76, p<0.001, I^2=82.9% [73.5%; 89%]; normal length of interval I–V for the term-born population at 40wks postconceptional age is 5.02ms[32]). The effect size of the mean difference in the I to V interval was moderate (0.574). The mean difference in the III to V interval (ΔABR=0.081ms) covers the mean difference in the I to V interval (ΔABR=0.073ms) completely. The forest plot in Figure 2 shows results of the III to V interval for all study groups, in descending order based on GA. Latency of peak V was also significantly delayed in infants born preterm (ΔABR=0.112, 95% CI=0.058– 0.165ms, p<0.001). Latency of peak I was also significantly delayed, but with a higher p-value (ΔABR=0.048, 95% CI=0.008–0.087ms, p=0.01).

We checked for a publication bias with Eggler's test, via a linear regression test of funnel plot asymmetry. The p-values of this test for the I to V and III to V intervals were not significant (I–V: p=0.13; III–V: p=0.32).

The effects of NICU treatment and GA on the difference (Δ_i) between preterm- and term-born infants were modelled via a linear random effects meta-regression, as introduced in the statistical analysis section. The results are presented in Table 2. Both NICU treatment and lower GA correlated with a longer III to V interval.

Figure 2. III–V interval.

Study	Pre-term	Term	Max GA	NICU	Delta
5	29	29	37	1	0.05
2	30	36	36	0	0.02
7B	35	41	36	0	0.05
8	39	37	36	0	0.05
9	31	35	36	0	0.04
10	111	92	36	0	0.00
3	52	37	36	1	0.10
4A	73	38	36	1	0.18
7A	68	41	36	1	0.08
11	163	49	36	1	0.12
4B	37	38	35	0	0.10
14	65	56	35	0	0.06
1	70	22	35	1	0.19
6	39	21	34	1	0.23
13	30	38	32	0	0.09
12	62	42	32	1	0.13
Summary					**0.08**

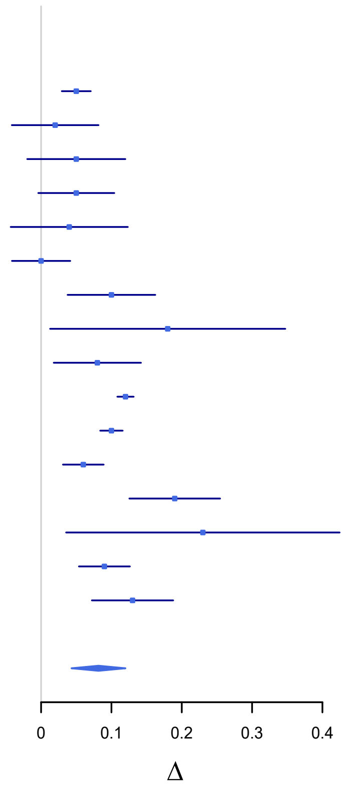


Table 2. Differences between preterm-born and term-born infants for the III-V interval for β1: intercept; β2: effect of NICU treatment; β3: effect of GA. Both variables individually affect the found difference between preterm-born and term-born children. However, it is important to note that the NICU variable is a binary variable and GA is continuous.

Variable	Parameter estimate	Parameter 95% CI	p-value
Intercept	0.627	0.070 to 1.153	0.01
NICU	0.062	0.021 to 0.108	0.021
GA	-0.016	-0.030 to -0.008	0.003

Discussion

This meta-analysis strongly and unambiguously showed that normal-hearing infants born preterm compared to healthy term-born infants have a significantly delayed auditory conduction from cochlea to brainstem at term age. The delay is seen in the III to V interval, and also reflects in the I to V interval. Thus, conduction delay arises mainly or even exclusively in the auditory brainstem. This confirms our initial hypothesis that exposure to the extra-uterine environment in the third trimester of pregnancy slows down conduction of electrical signals in the auditory brainstem, reflected by the III to V interval.

Two independent factors related to preterm birth were analyzed: GA and the need for NICU treatment. The effect of GA on ABR differences between preterm-born and term-born infants was statistically significant. Greater differences in conduction time were found in infants born preterm with lower GA. This suggests that a longer period of extra-uterine development leads to greater impairment of auditory brainstem development. The effect of GA on auditory maturation was investigated by using the maximum GA of each study group because, as explained earlier, there were no missing data of this variable. Consequently, all individual infants per study group were born before that maximum GA, which means that the real GA can be expected to be lower in a number of cases. Therefore, the real effect of GA on auditory brainstem is likely to be even stronger.

The need for neonatal intensive care was used as an indicator of the child's physical condition in the neonatal period. The effect of the need for NICU treatment was also significant, which means that medical complications affect development of the auditory brainstem. It is important to realize that cases with clear brain damage, such as perinatal asphyxia or an increased auditory threshold, had already been excluded from study groups of individual studies and therefore were not included in the meta-analysis. In future studies the influence of several neonatal complications could be studied separately and prospectively.

It seems likely that GA and the need for NICU treatment interact with and consolidate one another. However, in this meta-analysis these must be considered as two independent factors influencing the auditory brainstem development.

The different effects of the need for NICU treatment and GA are well illustrated in Figure 2. In nine of the 16 study groups, the maximum GA was 36 weeks. In four of these nine groups, the infants born preterm needed NICU treatment, and in these groups the delay in ABR was greater than in the groups where NICU treatment was not needed, which shows that NICU treatment affects ABR independently to GA. To provide more evidence for this point, a post-hoc analysis showed that the interaction between the two variables is not statistically significant. Further research should determine to what extent these factors interact and how this affects the maturation.

In the current meta-analysis we included only studies reporting measurements at term age. Therefore, we cannot show whether differences in auditory conduction between preterm-born and term-born infants will be sustained later in life. However, Coenraad et al. described the morphology of ABR in very preterm children (26wks postconceptual age) and concluded that latency of peak III was already identifiable, but latency of peak V was not (11). Peak V was only identifiable from 30 weeks postconceptual age. The few studies measuring ABR in children born preterm at later ages – 1 to 8 years – concluded that there is no significant difference with term-born children at those ages (20,21). Therefore, it is plausible that the delay in the III to V interval at term age is caused by a temporary maturational delay. Exposure to the extra-uterine environment in the third trimester of pregnancy slows down the myelination process, which is responsible for rapid synchronized conduction along the nerve (10,11).

Children born preterm often experience long-term developmental problems later in life (3–5). It has been proposed that delayed ABR interpeak latencies at an early stage reflect the general atypical neural (axonal) maturation that is responsible for these problems (8,9). Geva et al. also highlighted the importance of brainstem development in later development (37). They used ABR measurement to determine whether an infant had normal or compromised brainstem function, and concluded that compromised brainstem function canalized behavioural inhibition in children born preterm at 12 months of age. This would suggest that ABR latencies can be used as a marker for later developmental problems. Moreover, relatively subtle differences in maturation of the auditory brainstem at term age may represent even greater differences in maturation of more central parts of the brain, which cannot be measured with ABR. Lastly, the delay in maturation could also be causing a 'knock-on effect': a subtle delay at birth may be the beginning of developmental problems that increase over time, eventually to affect more complex functions concerning the central brain. Longitudinal research is needed to study the relationship between auditory conduction delay in newborn infants and several developmental problems later in life.

A possible limitation of the present meta-analysis is the number of articles from the same group. Ten of the 14 articles were written by the same first author (Jiang ZD). Part of the subgroup of infants born at term in the control group in Jiang et al (24) and Jiang et al (35) was the same as a part of that in the control group of Jiang et al (29). However, Jiang explicitly noted that the children born preterm included in his studies are all unique. Besides, these studies all used reliable, valid, and comparable designs, which makes our meta-analysis sample only more consistent. Also, there are several minor methodological variables that differ between studies, e.g. click rate, filter settings, and choices of measuring right or left ear. To maintain sufficient statistical power, acceptance of a certain amount of variation was inevitable. However, we limited these variations by including only case–control designs and analyzing only differences between groups within the same setting. Also, only interval data is included in the meta-analysis. Interval data is less sensitive to temporary peripheral auditory problems and to differences in measurement conditions than separate peak latency data. Small equipment-based differences are hereby eliminated. There is no clear evidence about the effect of other minor setting differences that could significantly have affected our results. However, a stricter standardization of the measurement procedures worldwide is needed to make ABR results more useful for scientific research.

This meta-analysis revealed that conduction time along the brainstem auditory pathway at term age in normal-hearing infants born preterm is delayed compared to term-born controls. This effect is mostly pronounced in the central conduction of the auditory pathway, concerning the brainstem. This finding suggests an abnormal maturation of the brainstem in infants born preterm, which can influence later development. The need for NICU treatment in the neonatal period is associated with abnormal auditory maturation in children born preterm. Also, GA of infants born preterm affects the maturation significantly; lower GA leads to greater delays in the auditory conduction. Future research may clarify the relationship between delayed maturation at term age and later developmental problems in children born preterm.

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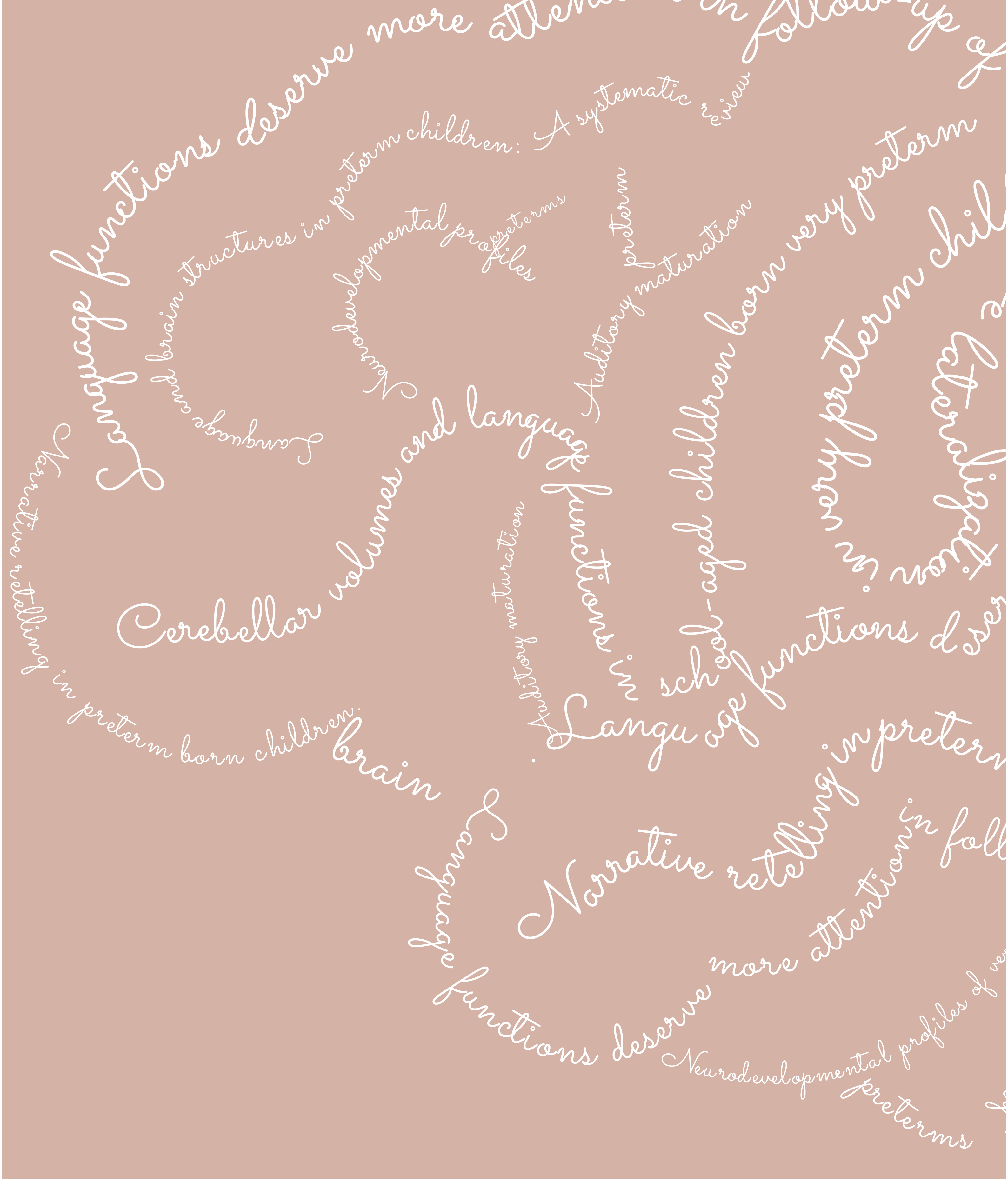
Language functions deserve more attention in follow-up of
Language and brain structures in preterm children: A systematic review
Neurodevelopmental profiles preterms
Auditory maturation preterm
Cerebellar volumes and language functions in school-aged children born very preterm
Lateralization in very preterm children
Narrative retelling in preterm born children.
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Chapter 3

Language outcome related to brain structures in school-aged preterm children: A systematic review

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Jeroen Dudink

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ABSTRACT

Aim

Preterm children often have language problems. This atypical language development is probably due to atypical brain development. We conducted a systematic review to provide an overview of the extensive and diverse scientific literature on the relations between language outcome and underlying brain structures in school-aged preterm-born children.

Method

Embase, Medline Ovid, Web of Science, Cochrane central and Google scholar were searched for relevant studies. Inclusion criteria were: cases are school-aged preterm children; structural MRI (T1- and T2-weighted sequences) or DTI used in combination with a neurocognitive language test; publication in an English-language peer-reviewed journal. Correlational measures between language scores and brain volume or fractional anisotropy of a brain structure were extracted.

Results

23 studies were included. The relations between oral language, verbal fluency and/or written language and MRI/DTI measurements of white matter, gray matter, cerebellum, corpus callosum and/or the fasciculi are presented. Oral language skills and verbal fluency appear to be related to the corpus callosum. Oral language skills are also related to the uncinate fasciculus. There seems to be no clear relation between cerebellar development and verbal fluency skills.

Conclusion and Implications

Not one single brain area is responsible for atypical language development, but several brain areas and their connections are essential. For future research it is recommended to relate brain areas to oral language skills on a microstructural level in preterm children. We also recommend to use language tests in which it is possible to distinguish between several language domains, such as perceptive and expressive language.

Introduction

Technological advances and combined efforts of obstetricians and neonatologists have resulted in improved survival for preterm infants (1). Nowadays, very preterm children (<32 weeks) represent 1%-2% of all live births in developed countries (2). These children are at risk for neurocognitive deficits even later in life. Depending on gestational age and neonatal complications, up to 30% of very preterm survivors in developed countries will experience significant long-term neurodevelopmental problems, such as cognitive, motor or hearing impairment (3). Subtler neurodevelopmental impairments, such as language disorders, learning disabilities, attention deficits, behavioral problems and social-emotional difficulties, occur even more often (3-9). Almost 20% of very preterm children are diagnosed with language disability at school age (6 to 17 years) and more than 50% require additional education (10). Two recent meta-analyses showed that problems with complex language functions, such as storytelling, even increase at ages 3 to 13 years (6, 11). These outcomes are alarming since language development is extremely important for academic achievements and communication in everyday life.

The atypical language development in preterm children is most likely a consequence of atypical brain development (10, 12). Several magnetic resonance imaging (MRI) studies showed macrostructural (e.g. measurements from T1- and T2 weighted structural MRI sequences) and microstructural (e.g. diffusion weighted MRI sequences) deviations in brain development in preterm children in childhood and adolescence (12). As compared to term-born controls, very preterm children had significantly smaller total brain volume, white matter volume, gray matter volume, cerebellum, hippocampus and corpus callosum. Furthermore, preterm birth is associated with a reduction in cortical folding. In a recently published systematic review of the association between very low birth weight (VLBW) and brain structures and cognitive function impairments, the authors concluded that both brain structures and cognitive functions are more often atypically developed in VLBW children (13). However, they did not look for association measurements between these two parameters and they did not include language outcome. Therefore, the association between atypical brain development and language skills remains unclear. Recently Kwon et al. reviewed literature about association measures between functional connectivity and language disorders (10). The authors suggest that there are alterations in the functional organization of language in preterm children and that these alterations in the developing brain are both proximate and long lasting. However, to our knowledge no systematic review has been published about association measures between structural MRI measures and language development in preterm children, whilst many studies have addressed relations between different MRI brain structures and several language domains. These MRI studies are diverse, however, since they focus on the relation between two measurements (language outcomes and brain structure measurements), which both can vary. A clear overview of all these results could be of great use to clinicians and researchers in the field.

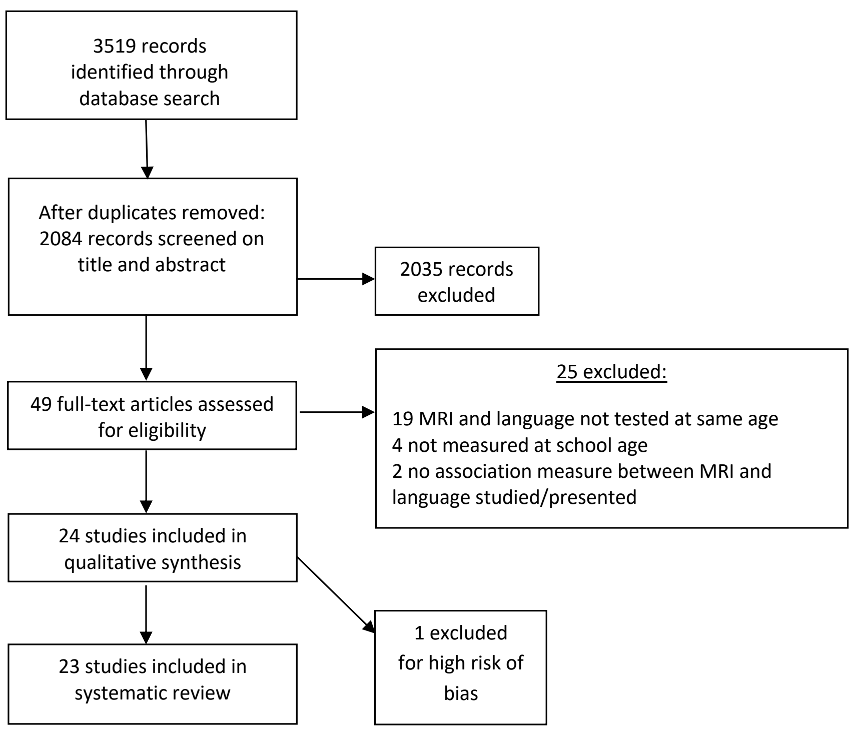
It can contribute to a better understanding of the actual relations between language and the brain in preterm children and set directions for consistent and high-quality research. Hence, the aim of the systematic review presented here is to provide an overview of what is currently known about language outcome of school-aged preterm children and the associations with their brain structures measured on MRI.

Method

Selection of studies

The computerized Embase, Medline Ovid, Web of Science, Cochrane central and Google scholar databases were searched for articles in January 2017 (and again in September 2017 to detect recently published articles) combining the search terms neurological, neurophysiology, neurobiology, forebrain, brain AND speech, language, verbal, linguistic, reading, writing, literacy, illiteracy, vocabulary, grammar, phonology, dyslexia AND premature, prematurity, preterm, "low birth, birthweight", "small*gestational age". In Figure 1 the flow diagram of the study selection is presented. The search yielded 2083 unique articles. Based on screening of titles and abstracts, 2035 articles were excluded. 49 articles remained and were assessed for eligibility based on the following exclusion criteria: (1) study cases are not school-aged children (6-17 years) born preterm (gestational age (GA) <37 weeks); (2) brain structures not measured with structural MRI (T1- and T2-weighted scans) and/or DTI; (3) language not assessed at the same age as the MRI scan

Figure 1. Flow diagram of study selection.



was made; (4) no correlational measure is published between language and brain volume or fractional anisotropy of a brain structure; (5) not published in an English language, peer-reviewed journal; (6) no sufficient study quality according to the Newcastle-Ottawa Quality Assessment Scale for cohort studies (44). A total of 25 studies had to be excluded based on these criteria, which resulted in 24 studies that were suitable for our data extraction and analysis (23 originally in January 2017, and 1 added in September 2017). Subsequently, one study was excluded since there was high risk of bias (14); the population and main outcome measure of this study were overlapping with those of one of the other included studies (15). Of these two studies, we included the most recently published one (15). The main characteristics of the final 23 included studies are presented in table 1.

Quality Assessment

Two authors (LS and JD) independently assessed the methodological quality of the included studies according to the Newcastle-Ottawa Quality Assessment Scale for cohort studies (44). This scale assesses the quality of cohort studies from the selection of the population, the comparability of the study groups and the ascertainment of outcome of interest. The total rating score ranges from 1 to 9, with 9 being the most favorable. Any disagreement between the two assessors with regard to the total score was resolved by discussion. Overall quality was rated from 5 to 8 stars.

Outcome Measures

Language outcome

Language is a very complex phenomenon which encompasses many different subdomains. Most language tests represent only one of these subdomains, assessed by associated language tasks. Therefore, not all language studies can be compared in a single, consistent way. Only studies that used the same language task, or comparable ones measuring the same language domain, can be validly compared. For example, composing and speaking a complex sentence is a task that is completely different from summing up words that start with an F, or spelling individual words – each of these three tasks requires skills from a specific language domain. Inevitably, the language tests used in the included studies vary widely. To be able to still validly compare study results we created three categories:

Oral language

This category includes tests that assess oral language ability, such as word and sentence comprehension and production, and vocabulary. Included tests are: Clinical Evaluation of Language Fundamentals-4 (CELF); Illinois Test of Psycholinguistic Abilities (ITPA); Morphological Test (MT); Peabody Picture Vocabulary Test (PPVT); Test for Reception of Grammar (TROG); Token Test for Children (TTC); Verbal scale of Wechsler Intelligence Scale for Children-III (WISC); verbal scale of Wechsler Adult Intelligence Scale (WAIS); verbal scale of Wechsler Preschool and Primary Scale of Intelligence (WPSSI).

Table 1. Study characteristics. In the correlation column, a '+' refers to a positive correlation; a '-' refers to a negative correlation; a '0' refers to no significant correlation.

Author/year of publication	Population PT (N) FT (N)	GA/ Birthweight	Major Exclusion criteria	Age at test (years)	Features MRI	Outcome measure MRI	Outcome measure Language	Correlation
Gäddlin et al.(16) 2008	PT: 59 FT: 57	<30 weeks	Down syndrome	15	T1, T2 (6 different hospitals)	WM injury 4-point scale	Oral language (WISC) Written language: reading	0
Yliherva et al.(17) 2001	PT: 41 FT: 24	26-35 weeks	Rett syndrome Duchenne dystrophy	8	1,0 T1	WM injury 4-point scale	Oral language (ITPA, MT, TTC)	0
Rushe et al.(18) 2001	PT: 75 FT: 21	<33 weeks	NA	14-15	GE 1,5 T1, T2	Injury 3-point scale	Verbal Fluency (FAS, Object and Animal naming, BNT) Written language (SGRST)	0
Skranes et al.(19) 1997	PT: 18 FT: 0	<1500 gram	Disabled children (such as CP)	6	Philips 1,5 T1, T2	Presence of periventricular gliosis, loss of white matter, ventricular dilatation and cortical atrophy	Oral language (WPSSI)	0
Isaacs et al.(20) 2004	PT: 65 FT: 0	28,5 (1.2)	Neuromotor or neurosensory impairment	12-16	Siemens 1,5 T2	Brain volumes	Oral language (WISC)	WM: +par/temp, –fr *(VBM correlations: 39, -69, 28; p <.01)* GM: –par, +fr *(VBM correlations: ±40, –70, 30; p<0.01)*
Nosarti et al.(21) 2008	PT: 207 FT: 104	<33 weeks	For controls: any history of neurological conditions including meningitis, head injury and cerebral infections	14-15	GE 1,5 T1	Brain volumes	Verbal Fluency (FAS, Object and Animal naming)	WM: +fr/temp GM: –fr/temp *(29% of variance: F=2,3; p<0.0001)*
							Written language (SGRST)	WM: +fr/temp, GM: –fr/temp *(28% of variance F=2,3; p<0.0001)*
McCoy et al.(22) 2014	PT: 26 FT: 0	27,81 (2.0)	Inclusion: liberal transfusion group	13	Siemens 3,0 T1, T2	Brain volumes	Verbal Fluency (COWAT)	WM females: +temp *($r^2 \Delta$ = .237; p<.05)* Cerebellum: 0
Scott et al.(23) 2011	PT: 218 FT: 127	<33 weeks	NA	14-15	GE 1,5 T1, T2	Brain volumes	Verbal Fluency (COWAT, Object and Animal Naming)	WM: 0fr
							Written language (SGRST)	WM: 0fr GM: +fr *(z-score 4.98; p<.05)*

Arhan et al.(24) 2017	PT: 22 FT: 24	28-33 weeks	Apgar score at 5 min >7; absence of major neonatal morbidity; absence of cerebral pathology such as IVH	9	Siemens 1,5 T1	Cerebellum and CC volume	Oral language (WISC)	Cerebellum: + *(Subtest comprehension: r =.93; p=.001)* CC: + *(subtest vocabulary: r =.91; p=.001)*
Parker et al.(25) 2008	PT: 65 FT: 34	<33 weeks	IVH, drug exposure during pregnancy	15	GE 1,5 T1	Cerebellum volume	Oral language (WISC)	+ *(r =.401; p=.008)*
							Verbal Fluency (COWAT, Object and Animal Naming)	0
Narberhaus et al.(26) 2008	PT: 52 FT: 52	<33 weeks	IQ < 70, history of traumatic brain injury, CP or other neurological diagnosis, motor or sensory impairment that precluded neuropsychological assessment	10-19	GE 1,5 T1	CC volume	Oral language (WISC/WAIS subtest)	+ *(for splenium :r = .32; p<.05)*
							Verbal fluency (COWAT)	+ *(for genu: r = .37; p<.01)* *(for splenium: r =0.32; p<.05)* *(for isthmus: r = .28; p<.05)*
Nosarti et al.(27) 2004	PT: 66 FT: 51	<33 weeks	NA	14-15	GE 1,5 T1, T2	CC volume	Oral language (WISC)	+ *(for mid-posterior CC: β = .33; p=.009)*
							Verbal fluency (COWAT, Object and Animal Naming)	+ *(total CC:β = .35; p=.006)*
							Written language (SGRST)	0
Allin et al.(28) 2001	PT: 67 FT: 50	<33 weeks	NA	14-15	GE 1,5 T1	Cerebellum volume	Verbal Fluency (FAS, BNT)	0
							Written language (SGRST)	Reading: + *(β = .295; p=.019)* Spelling: 0
Martinussen et al.(29) 2009	PT: 50 FT: 49 SGA: 49	29,1 (2.7)	NA	15	Siemens 1,5 IR	Brain volumes	Oral language (WISC)	0 WM and Cerebellum: +SGA *(Stepwise regression: step 2, part r =.1066, F value = 6.53; p=.0142)*
	PT: 52	34-36 weeks	Multiple birth, major medical disease,	6 -13	Siemens 3,0		Oral language (WISC)	0

Brumbaugh et al.(30) 2016	FT: 74		neurological injury, 5-minute Apgar score <7, neonatal sepsis, and birth weight <1500 g for late PT children and <2500 g for FT children		T1	Brain volumes (WM, Cerebellum)		
							Verbal Fluency (BNT, Object Naming)	0
							Written language: reading (WRAT)	0
Caldú et al.(31) 2006	PT: 25 FT: 25	<33 weeks, 29.48 (2.52)	Mentally or physically disabled children	13	GE 1,5 T1	GM, WM and CC volume	Oral language (WISC/WAIS),	WM: 0 GM: + *(r = .50; p<.05)* CC: 0
							Verbal fluency (RAVLT)	WM: 0 GM: 0 CC: 0
Northam et al.(32) 2012	PT: 50 FT: 30	<33 weeks. 27(2)	NA	16	Siemens 1,5 T1, T2	Brain volumes (CC, Fasciculi)	Oral language (PPVT, TROG)	CC: + *(Ancova F(2.72)= 20.5 p<.0001)* UF: + AF: 0
Mullen et al.(33) 2011	PT: 44 FT: 41	28,3 (1.9)	IVH, PVL, low pressure ventriculomegaly, abnormal MRI findings, abnormal total ventricular CSF volume	16	Siemens, 1,5	Brain volumes	Oral language (WISC, PPVT)	WM: 0 AF: 0 UF: + *(left: r=.314; p=.038,* *right: r=.336; p=.026)*
							Verbal Fluency (CTOPP)	AF: + *(left: r=.424; p=.004,* *right: r=.301; p=.047)* UF: 0
Andrews et al.(34) 2010	PT: 19 FT: 9	24-36 weeks 30,5 (3,2)	NA	11	Siemens 3,0 T1	DTI	Written language : reading (WJTA)	Temp/par: + *(for passage comprehension:* *left: r=.417; p<.05,* *right: r=.459; p<.05)* CC: + *(for word identification:* *r=.553; p<.05* *for word attack: r =.537; p<.05)*
Constable et al.(35) 2008	PT: 29 FT: 22	28,4 (2,0)	IVH, WM injury and/or ventriculomegaly	12	GE 1,5 SPGR	DTI	Oral language (WISC, PPVT-R)	UF: +males *(for VIQ left: r=0.513; p=.051, right: r=.635; p=.008* *for PPVT left: r=.511; p=.052, right: r=.619, p=.011)* UFright: –females *(for VIQ : r=-.744; p=.004* *for PPVT: r=-.759, p=.003)*

Kontis et al.(36) 2009	PT: 63 FT: 45	<33 weeks	Left-handedness	15	GE 1,5	DTI	Oral language (WISC)	CC: 0
							Verbal Fluency (CVLT)	CC: + *(for CC body with intrusions item: r=.295; p=.029* *for Splenium with short delay: r=.312, p=.020* *for splenium with long delay: r=.273 p=.0.44* *for splenium with long delay free recall: r=.313, p=.020* *for splenium with intrusions: r=-.306, p=.023)*
Skranes et al.(37) 2007	PT: 34 FT: 47	29,3 (2.7)	Trisomy 21	15	Siemens 1,5 T1	DTI	Oral language (WISC)	SLright: + *(r=.363; p<0.05)*
Travis et al.(15) 2016	PT: 26 FT: 19	26,0-34,5	Active seizure disorder, hydrocephalus, receptive vocabulary score < 70, sensorineural hearing loss, and non-native speaker of English	9-17	GE 3,0 T1	DTI	Written language: reading (WJTA; BRSC)	AFleft: + *(for decoding: r=.606; p<.05)* *UFleft: +* *(for comprehension: r=.562; p<.05)* SL: + *(for decoding: right: r=.403; p<.05), left: r=.466; p<.05* *for comprehension: left: r=.417 p<.05)*

Abbreviations: AF=arcuate fasciculus; CC=Corpus Callosum; CSF=cerebrospinal fluid; f=females; fr=frontal lobe; FT=full-term; GE: General Electric; GM=gray matter; m=males; IVH=Intraventricular hemorrhage; NA=not applicable; L=left; par=parietal lobe; PT=preterm; PVL=periventricular leukomalacia; R=right; read=reading; SGA: small for gestational age; SL=superior longitudinal fasciculus; spel=spelling; spl=splenium; temp=temporal lobe; UF=uncinated fasciculus; WM=white matter.

Verbal fluency

This category includes tests that assess verbal (phonetic or semantic) fluency, which requires special use of executive functions in combination with language functions: Boston Naming Test (BNT); Controlled Oral Word Association Test (COWAT); Comprehensive Test of Phonological Processing (CTOPP); California Verbal Learning Test (CVLT); FAS-test; Object and Animal naming; Rey Auditory Verbal Learning Test (RAVLT); Stroop test TBAG version.

Written language

This category includes tests that target reading and spelling: Basic Reading Skills Cluster (BRSC); Schonnel Graded Reading and Spelling Test (SGRST); reading subtests of the Woodstock-Johnson III Test of Achievement (WJTA); reading score of Wide Range Achievement Test (WRAT).

MRI

We related language outcome in the above-mentioned three categories to the underlying brain structures. Different brain structures can be reliably measured in-vivo on structural (anatomical) T1- and T2-weighted MRI sequences – either manually, semi-automatically or automatically. Different software post processing tools are available for this purpose, allowing macro-structural measurements of brain structures. Diffusion tensor imaging (DTI) sequences allow visualization and quantification of white and gray matter microstructure. Several diffusion parameters can be derived from DTI results, but white matter integrity is most commonly estimated with fractional anisotropy (FA). FA is a scalar value between 0 and 1 describing the amount of diffusion asymmetry (anisotropy) within a voxel, defined in terms of its eigenvalues. FA=0 means that diffusion is isotropic (i.e. it is unrestricted or equally restricted in all directions). FA=1 means that diffusion occurs along one axis only and is fully restricted along all perpendicular directions.

Data Extraction

For each included study we extracted the published correlational measures between language scores and brain volume or fractional anisotropy of a brain structure. Most of the studies reported a Pearson's correlation coefficient. A few studies also reported Spearman's rho or stepwise logistic regression analyses as a correlation measure. The correlational measure had to correlate a language score (classified within one of the three categories discussed above) and a brain area that is addressed in at least two different studies. For example, total brain volume, brainstem volume and cerebral spinal fluid (CSF) were all studied only once (29-31), and therefore the respective findings are not presented in the cross table. Besides, these studies explicitly reported that they did not find any significant relations with language.

Results

Four of the 23 included studies (16-19) addressed the relation between children's language skills and white matter injury only, classified on either a 3- or 4-point scale. None of these studies found a significant association between this damage classification and language skills.

The remaining 19 studies used brain volume measurements or DTI to relate brain structures to language outcomes. A cross table (table 2) shows the associations between language skills and brain structures reported in these 19 studies. A '+' refers to a positive correlation, a '–' to a negative correlation and a '0' to no significant correlation.

Oral Language

White and gray matter volume

Five studies reported findings about total white matter (WM) and/or gray matter (GM) volumes and the correlation with oral language scores (20, 29-31, 33). Four studies (29-31, 33) explicitly reported no significant correlations with WM volume in preterm children. However, one of these (29) did find a significant correlation for small for gestational age (SGA) children. Also, two studies (20, 31) found significant correlations in preterm children; the authors emphasized that these correlations are based on complicated, specific patterns of cortical and subcortical alterations. For example, Isaacs et al. described a positive correlation with WM volume in specific areas of the parietal and temporal lobes, a negative correlation between language and WM volume in frontal lobe areas, a negative correlation with GM volume in the parietal lobe and a positive correlation with GM volume in the frontal lobe (20). Thus, both positive and negative correlations between oral language and GM and WM volume in different cortical areas were found.

Corpus callosum volume

Six studies described a relation between the volume of the corpus callosum (CC) and oral language skills. Four of them presented a positive correlation (24, 26, 27, 32). Arhan et al. (24) even show a correlation of $r = 0.91$; $p = 0.001$, which can be interpreted as very strong. Caldu et al. (31) and Kontis et al. (36) did not find a significant correlation between oral language skills and CC volume.

Cerebellum volume

Four studies associated cerebellar volume with oral language skills. Arhan et al. (24) and Parker et al. (25) described a positive correlation between oral language skills and cerebellar volume in preterm children. Arhan et al. again show a very strong association ($r = 0.93$; $p = 0.001$). Two studies did not find a correlation in preterm children (29, 30). Martinussen et al. (29) did find a correlation in SGA children though.

DTI measurements Fasciculi

Five studies reported findings about the association between oral language skills and the fasciculi in the brain. None of the studies reported a significant relation between oral language skills and the arcuate fasciculus (AF). Moreover, two studies reported explicitly that no significant relation was found between oral language skills and the AF (32, 33). However, three studies reported a significant positive relation between oral language and the uncinate fasciculus (UF) (32, 33, 35). The correlations presented by Constable et al. (35) are worth to note specifically, since the associations they found were strong (for example $r = -0.759$; $p = .003$ for the association between PPVT scores and the right UF in females). One study reported a significant positive relation with the superior longitudinal fasciculus (SLF) (37).

Verbal fluency: language and executive functioning

White and gray matter volume

Five studies reported findings about the relation between WM and/or GM volume and verbal fluency skills. Two of these studies described a significant correlation (21, 22). The one by McCoy et al. (22), found a positive correlation in females, in higher temporal white matter. The other, by Nosarti et al. (21), found a positive correlation between WM volume in frontal and temporal regions and verbal fluency and a negative correlation between GM volume and verbal fluency. The other three studies did not find any correlation between verbal fluency and GM or WM volumes (23, 30, 31).

Corpus callosum volume

Five studies reported findings about the correlation between CC volume and verbal fluency. Three studies (26, 27, 36) described a positive correlation. However, Caldu et al. (31) did not find any correlation between CC and verbal fluency.

Cerebellum volume

None of the four studies that described the relation between cerebellar volume and verbal fluency found any correlation (22, 25, 28, 30).

DTI measurements Fasciculi

Only Mullen et al. (33) reported about the relation between fasciculi and verbal fluency and found a significant positive correlation with the left and right AF and no correlation with the UF.

Written language: reading and spelling

White and gray matter volume

Four studies reported findings about GM and/or WM volume in relation with written

Table 2. Study results. A '+' refers to a positive correlation; a '–' refers to a negative correlation; a '0' refers to no significant correlation.
Abbreviations: CC=Corpus Callosum; f=females; fr=frontal lobe; GM=gray matter; m=males; L=left; par=parietal lobe; R=right; read=reading; SGA: small for gestational age; spel=spelling; spl=splenium; temp=temporal lobe; WM=white matter.

	WM volume	GM volume	CC volume	Cerebellum volume	DTI measurements Fasciculi		
					Arcuate	Uncinate	Superior Longitudinal
Oral language	+SGA(29), +par/temp(20), –fr(20)	+(31), +fr(20)–par(20)	+spl(26), +(27), (24, 32)	+SGA(29), +(24, 25),		+(32, 33)L/R, +m(35), –f R(35)	+R(37)
	0(29, 31),(30),(33)		0(31, 36)	0(29),(30)	0(32, 33)L/R		
Verbal Fluency (executive functioning and language)	+fr/temp(21) +temp_f(22)	–fr/temp(21)	+(26, 27, 36)		+(33)L/R		
	0(30, 31), 0fr(23)	0(31)	0(31)	0(22, 25, 28, 30)		0(33)L/R	
Written language: (reading/spelling)	+fr/temp(21) +temp/par(34)	–fr/temp(21) +fr(23)	+(34)	+read(28)	+L(15)	+L(15)	+L/R(15)
	0(30), 0fr(23)		0(27)	0(30), 0spel(28)			

language skills. Nosarti et al. (21) found significant correlations in the temporal gyrus: negative correlation with GM volumes and positive correlation with WM volumes in females only. Andrews et al. (34) also found a positive correlation in temporal parietal regions between reading and WM volume. Scott et al. (23) presented a positive correlation between GM volume in frontal lobe regions and no correlations, however, with WM volumes. Brumbaugh et al. (30) did not find significant correlations between WM volume and written language skills.

Corpus callosum volume

Andrews et al. (34) found a significant correlation between fractional anisotropy in the CC and reading skills. On the other hand, Nosarti et al. (27) did not find any significant correlations between CC volume and written language skills.

Cerebellum volume

Allin et al. (28) found a positive correlation between reading skills and cerebellar volume, but not between spelling skills and cerebellar volume. Brumbaugh et al. (30) did not find a correlation between reading and cerebellum volume.

DTI measurements Fasciculi

Only one study, by Travis et al., described correlations between fractional anisotropy in the fasciculi and written language skills (15). Correlations were found with reading and spelling and the left AF and left UF.

Discussion

Main findings

Our overview of study results in language and brain structure associations in preterm children yielded a complex set of relations, of which some show more consensus than others. We will discuss the most remarkable results.

Perhaps most notable is the lack of any association between structural brain injury and language outcomes. We had expected that preterm children with explicit brain damage would have the most severe language problems. However, in these studies brain damage was scored on a 3- or 4-point scale and naturally, in all studies the group of children with explicit damage was relatively small compared to groups of children with less damage, which makes it hard to prove a correlation with language. This might have influenced the correlations found between language skills and brain damage.

Another remarkable result concerns the cerebellum volume. We studied three language domains (i.e. oral language, verbal fluency and written language) and only very few studies found a significant correlation between any of these domains and the volume of the cerebellum; no correlation at all was reported for verbal fluency. A clear correlation between verbal fluency and cerebellar volume cannot be shown, and seems unlikely for both oral and written language.

The association of the CC volume with language outcomes is more convincing, particularly with regard to oral language skills and verbal fluency. Only one of the included studies did not find a significant correlation with language skills or verbal fluency (31), but this can likely be ascribed to insufficient statistical power, as this was the study with the smallest population of preterm children (n=25). Overall, an association between oral language and CC volume is likely. However, the relation between CC and written language skills remain inconclusive, since there were only two studies that reported correlational data between these measures and they reported opposing results (27, 34).

Regarding the DTI studies, the most striking result is the repeatedly reported significant correlation between UF and oral language skills. The UF is part of the ventral language pathway and in recent literature it is often associated with semantic language functions. However, there is a lack of evidence for a general role of the UF in language (38). Our review, though, showed a positive correlation between the UF and oral language skills. An association between language skills and the AF, which is part of the dorsal language stream, is less obvious according to our review results. Unfortunately, few studies included in our review addressed the role of the AF. Still, these tentatively show that the AF is more involved in verbal fluency, whilst the UF is more involved in oral language.

A less convincing result is the correlation between language and areas of WM and GM volume. Many studies did look at WM and GM in relation to one of the language domains, but the results were inconsistent. We propose that these kinds of differences between studies might arise because each addresses a slightly different microstructural area of the brain. When total WM or GM volume is studied, rarely any relation with language is found, while many significant relations are found when studying several microstructures of the brain. For example, Nosarti et al. (21) found a negative correlation between written language skills and GM volume in the temporal lobe, while Scott et al. (23) found a positive correlation in the frontal lobe. Overall we see that GM volume is more often negatively correlated with language skills, while WM volume mostly correlated positively with language skills. This negative association of GM with language corresponds with recent literature, also for example in stuttering literature (39), and has been associated with a cortical developmental phase of dendritic and synaptic pruning in late childhood and adolescence (40-43). This might mark a shift from relatively diffuse cortical representations of cognitive functions in early childhood toward a more accurate, efficient, and faster processing language system later on.

Oral language skills are more often significantly correlated to preterm brain structures compared to verbal fluency skills or written language skills (table 2). Thus, atypical brain development in preterm children seems to affect oral language more obviously than it affects verbal fluency or reading or spelling. This is interesting in the sense that verbal fluency skills are also based on executive functioning, while oral language skills are mostly language proficiency tasks. Apparently, brain structures of preterm children are associated more strongly with language tasks than with executive functioning based language tasks.

Influencing factors

It is plausible that gestational age (GA) is an important influencing factor in the relation between brain and language, where lower GA leads to more atypical brain and language development and a relation between these two parameters would be more obvious. However, the populations of almost all included studies consisted of very preterm children with a gestational age of <33 weeks. One study (30) included a population of late preterm children only (34-36 weeks GA). The authors did not find a correlation with language, which is in accordance with the idea that higher GA leads to less atypical brain and language development. However, this lack of correlation might be a consequence of the fact that only the cerebellum was studied, which in many of the other studies was not correlated with language. Because of these considerations we cannot indicate an effect of GA from our study results.

Another factor that might have been of influence is the MRI methodology used. Overall, studies that used DTI as a MRI measurement reported more significant correlations than studies that used volume measurements only.

A third factor to take into account is sex. Several included studies presented results for boys and girls separately. We analyzed these results to search for similarities in boys and girls, but did not find consensus within these results. Therefore, we cannot draw a general conclusion about the role of sex in the correlation between brain and language.

Strengths and limitations

The strength of this review is that it provides a clear overview of the most comparable studies on the relation between language and brain structure in school-aged preterm children. This is a very complex subject because it covers two crossing parameters, which each in itself is complex and variable. We achieved to keep the most important factors relatively stable, such as age of the population, MRI scanner features, language tests used and population size. Also, our classification into three language domain groups resulted in a structured overview. We hope that this categorization will contribute to the validity of future correlational studies of brain function and language outcomes.

A possible limitation of the study is the risk of publication bias, i.e. studies may have analyzed more regions in the brain than reported in the result section. To partly adjust for this, when a certain region was mentioned in the methods section, but not addressed in the results section, we interpreted this as: no significant correlation found. And then, of course, performed studies that did not find any significant correlations may not have been published at all. Therefore, we highlighted the results presented by at least two study groups. When only one study looked into a certain relation – for example the relation between written language skills and the fasciculi - we did not highlight the outcome in our review results and discussion.

In our systematic review we chose to focus on the most commonly used MRI and DTI methods (structural T1- and T2-weighted sequences MRI and DTI). However, there are already some new models, such as non-tensor-based diffusion imaging analyses (e.g. high angular resolution diffusion imaging (HARDI)) that are very promising. HARDI is a new advanced model, which is an improvement with respect to DTI because it can deal with crossing fibers in voxels. It is successfully used very recently in a study with preterm children at term equivalent age (44). The authors state that their findings suggest that differences in arcuate fasciculi micro-structure have a significant impact on language development and modulate the first stages of language learning. However, non-tensor-based diffusion imaging analyses were beyond the scope of our systematic review since the method is relatively new. Data are still limited and no studies are published in school-aged preterm children yet.

Implications for further research

For future research we would recommend to relate the brain on a microstructural level to oral language skills in preterm children. We would recommend to use language tests such as the CELF, since this test battery consists of a number of subsets that cover all oral language domains and can be subdivided in subcategories, such as perceptive and expressive language. We recommend to study these oral language subcategories separately and relate these and written language skills to brain structures. With respect to MRI/DTI measurements, longitudinal GM and WM analysis seems to be promising methods, highly relevant to longitudinal research in preterm children and the relation with their cognitive development. We also recommend to use non-tensor-based diffusion imaging analysis, since this new advanced model is an improvement with respect to DTI. Besides, we recommend to use principle component analysis (PCA) as an analytical approach, which might prevent random correlational findings and can actually lead to meaningful associations. PCA is a renowned method with a longstanding tradition which is now again increasingly and successfully being used in neonatal MRI studies to quantify the proportion of shared variance in the measured water diffusion parameters (MD, FA, λ_{ax} and λ_{rad}) across the tracts (45). Lastly, more consistent data collection and data sharing could lead to more and quality-assured knowledge in this research field.

Conclusion

This systematic review gives an overview of the extensive and diverse scientific literature on the associations between MRI brain measures and language outcome in children born preterm. Oral language skills and verbal fluency were shown to be associated with CC volume. Oral language skills are also associated with the UF. Overall, oral language skills are more obviously associated with several microstructural brain areas than are verbal fluency tasks, which are executive functioning based language tasks, and reading and spelling tasks. No associations were found between cerebellar volume and verbal fluency. The relation between oral language and written language with cerebellar development seems weak. The relation between preterm brain injury and language outcome could not be proven in studies that used brain damage scales. This most likely implies that not one single damaged brain area is responsible for atypical language development, but that several brain areas and their connections are essential. For future research we would recommend to study overall brain connectivity in combination with oral language skills, in which good quality management and data sharing will be crucial to enhance our shared knowledge and clinical opportunities.

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Language functions deserve more attention in follow-up of

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Neurodevelopmental profiles preterms

Auditory maturation preterm

Auditory maturation

children born very preterm

in very preterm children

Lateralization

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

Narrative retelling in preterm born children.

brain

Language functions deserve

Narrative retelling in preterm

more attention in follow

Language functions deserve more attention in

Neurodevelopmental profiles of very preterms

Chapter 4

Language functions deserve more attention in follow-up of children born very preterm

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ABSTRACT

Background

Language is a complex neurodevelopmental phenomenon. Approximately 45% of children born very preterm (VPT) show mild-to-severe language problems throughout childhood. Nevertheless, in most hospitals in Europe language functions are not routinely assessed at follow-up.

Objective

To give clear indications for extensive language assessment in school-aged children born VP, based on routinely assessed intelligence and behavioral problems.

Method

Language functions of 63 10-year-old children born VPT (<32 weeks' gestation) without major handicaps were compared to their intellectual and executive functions and behavioral problems. Using multiple linear regression analyses, the predictive value of perinatal factors and the association with neurodevelopmental factors of low language were measured.

Results

The mean language score was significantly lower than the verbal intelligent quotient (VIQ; mean difference=6.4, $p<.001$, $d=.48$) and the mean vocabulary knowledge (mean difference=9.3, $p<.001$, $d=.70$). Besides, VIQ (β = .649, $p=.001$) and performance IQ (PIQ; β = .260, $p=.035$) were significantly associated with language scores. Significant predictors of language scores were number of days of assisted ventilation (β = -.592, $p=.015$) and mother's vocabulary knowledge (β =.473, $p=.014$), rather than mother's educational level (β =.139, $p=.956$).

Conclusions

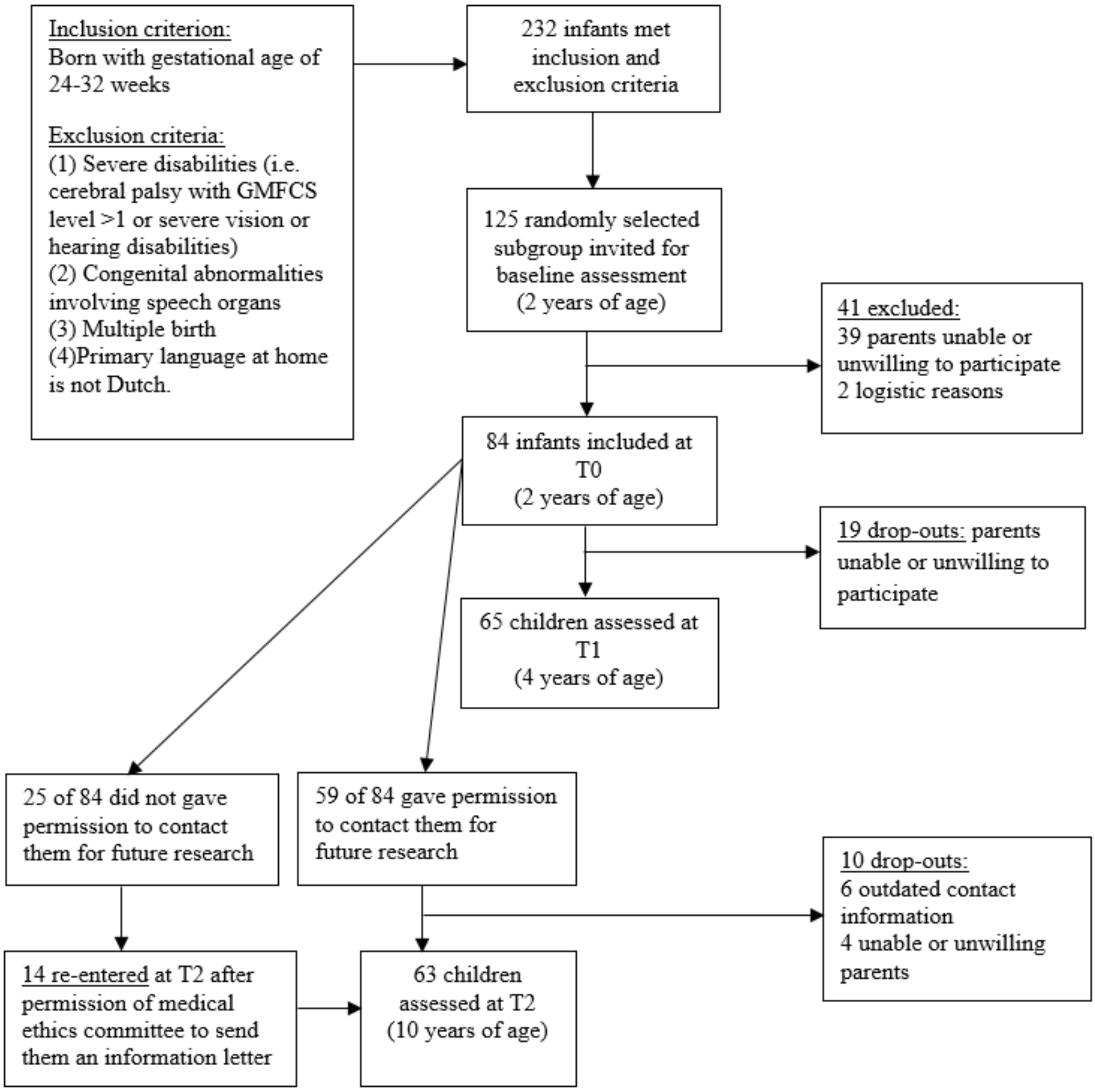
Children born VPT had language problems that were not expected from their significantly higher VIQ and vocabulary knowledge. Clinicians assessing these children should be aware of possible language problems, which cannot be detected with a simple vocabulary task. Our findings provide evidence of the need for adequate language assessments by a speech-language pathologist in children born VP, especially in those with VIQ scores in the low average range.

Introduction

In most hospitals in Europe relatively little attention is given to the assessment of language functions in clinical follow-up of children born very preterm (VPT, i.e. less than 32 weeks of gestation), which is in accordance with follow-up guidelines. For example, the English and Dutch guidelines suggest assessments by the neonatologist and psychologist at 2 and 4 years of age, but not by a speech-language pathologist (1, 2). Consequently, intellectual functions and behavioral problems are routinely assessed and language functions are not. However, language is a complex neurodevelopmental phenomenon, that is crucial to academic and societal achievement (3, 4). Many cross-sectional and longitudinal studies that adequately and extensively assessed language functions in school-aged children born VPT reported receptive and expressive language deficits in 22-45% of children born VP, even without genetic or congenital abnormalities (5-16). School-aged children born VPT in particular seem to show problems with more complex language functions, rather than with vocabulary knowledge (6, 7, 17). Since complexity of language use during childhood increases, the spontaneous language use of school-aged children might not be fully represented by vocabulary knowledge alone. Their language functions should therefore be assessed adequately and extensively. Nevertheless, language functions are still sometimes described on the basis of a set or subset of intellectual assessments, executive functioning assessments or a vocabulary test (18-23).

Mainly on the basis of intellectual functions, behavioral problem scores or sometimes vocabulary knowledge, the neonatologist and psychologist have to decide at follow-up meetings whether a speech-language pathologist needs to be consulted. Yet, when language functions are not optimally assessed, some (complex) language problems might remain unobserved. Therefore, the overall aim of this study is to provide evidence for guidelines that clinicians working with children born VPT can use at follow-up, to decide correctly whether or not a child is at risk for language problems and needs to be assessed by a speech-language pathologist. We formulated three objectives. First, to compare language functions to vocabulary knowledge, intellectual functions and behavioral problems. We hypothesized that language functions are not well assessed by means of intellectual functions, vocabulary knowledge or behavioral problems. Second, to measure the extent to which language functions are associated with other neurodevelopmental child factors. Neurodevelopmental deficits in children born VP, such as attention deficits and regulation problems, have been associated with academic achievement, including reading and spelling (24, 25). Attention problems have also been associated with oral language functions (26). It is still unknown, however, if and to what extent cognitive functions, behavioral problems and executive functioning are associated with oral complex language functions. Our third objective is to ascertain whether perinatal and familial factors can predict these language outcomes. While infants born extremely preterm (gestational age (GA) 24-28 weeks), boys and children of families with low social economic status (SES) are at higher risk of developing neurodevelopmental problems (27), it is unknown whether risk factors like these are also involved in language problems in school-aged children born VP.

Figure 1. Flow-chart of inclusion process of the cohort.



Materials and Methods

Participants

The present study concerns the cross-sectional data of 63 children at age 10 years (T2). They were part of a longitudinal cohort study of language and brain development in children born VPT and had been admitted to the NICU 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 Figure 1. Children that 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 (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. These criteria were checked during neonatal protocol examination by the pediatrician and psychologist 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, since its crucial impact on language functioning.

Procedure

The children's language, hearing threshold, cognition, executive functioning and behavioral problems and the parent's vocabulary knowledge were assessed during a one-day visit to the Erasmus-MC Sophia's Children's Hospital.

Language functioning was assessed with the Clinical Evaluation of Language Fundamentals, Fourth Edition (CELF-4) (28). The CELF-4 consists of 11 language subtests. Different combinations of these subtests form the Core Language Score and five index scores (i.e. Receptive Language index; Expressive Language index; Language Content index; Language Form index and Working Memory index). The Core Language Score is a composite of four subtests: Concepts & Following Directions; Recalling Sentences; Formulating Sentences; Word Classes (receptive and expressive). For all five language indexes a standard score was calculated based on a normally distributed scale with a mean of 100 and an SD of 15.

Vocabulary knowledge was assessed with the Peabody Picture Vocabulary Task-III (PPVT-III). This test measures receptive vocabulary knowledge based on spoken words accompanied by four pictures to choose from (29). After the inclusion of the first 9 children, we decided to also administer the PPVT-III word comprehension test to the parents. Of 54 of the included children, either the mother (n=45; 83%) or the father (n=9; 17%) was assessed, thereby providing a language-specific familial risk factor. The native language of all parents was Dutch. The PPVT-III provides a standard score based on a normally distributed scale with a mean of 100 and an SD of 15.

Intellectual functioning was estimated with the Wechsler Intelligence Scale for Children (WISC-III) (30). This test battery contains several subtests, summarized in a verbal intelligence quotient (VIQ), a performance intelligence quotient (PIQ) and a total intelligence quotient (TIQ), all based on a normally distributed scale with a mean of 100 and SD of 15.

Executive functioning was assessed by both a parent and a teacher report of the Behavior Rating Inventory Executive Functions (BRIEF) (31) questionnaire. The mean of the parents' and teachers' Behavioral Regulation Index scores was calculated as a measure of regulation problems.

Behavioral/Emotional Problems were assessed by using a parent and teacher report of the Child Behavior Checklist (CBCL/6-18) and the Teacher Report Form (TRF/-6-18) respectively (32). The mean of the mothers', fathers' and teachers' Attention Problems scale scores was calculated. Regarding the index scores of the BRIEF and CBCL/TRF, a score <60 was defined as normal; a score of 60-65 as subclinical; and a score >65 as clinical.

As hearing functioning can affect oral language functions directly, pure-tone audiometry (0.5, 1, 2 kHz) and tympanometry were performed to measure hearing thresholds, and observe possible hearing losses. All hearing measurements were performed in a soundproof booth. A computer-based clinical audiometry system (Decos Technology Group, version 210.2.6 with AudioNigma interface) and TDH-39 headphones were used.

All above tests were normed and validated for Dutch children and were performed by a trained clinician: language tests by a speech-language pathologist; intellectual functioning by a clinical psychologist; hearing functioning by a certified clinician according to the ISO standard 8253-1 [International Organization for Standardization, 2010].

Statistical analysis

Pearson's chi-square test was used to compare the number of children born VPT with below average Core Language Scores to that number in the population. A paired sample t-test was used to compare the children's mean Core Language Score to respectively the mean vocabulary score, the mean VIQ and the mean PIQ. The correlation between these variables was measured with Pearson's correlation coefficients. In addition, two multiple linear regression analyses (with forced entry) were done. A maximum of five independent variables could be included in the regression analysis, based on our number of patients (n=63). The first multiple regression analysis served to measure the extent to which other child factors at 10 years of age were associated with language scores. The following factors were entered: VIQ; PIQ; Attention Problems score and Regulation Index. The second analysis served to predict CL outcome at 10 years of age on the basis of perinatal and familial factors. GA, birthweight (BW), number of days of assisted ventilation and number of days at NICU are interdependent and the mutual correlations were all very high. Due to our limited sample size, we could only include one of these variables in our model. We selected number of days of assisted ventilation, since we think this measure reflects the overall severity of the preterm birth and following neonatal illness. The following independent variables were entered in the regression analysis: sex, number of days of assisted ventilation, mother's educational level and parent's vocabulary score. Since we only had parent's vocabulary score of 54 children, this regression analysis was based on the data of these 54 patients only.

Table 1. Language, intelligence, behavioral and executive functioning outcomes of children born VPT at 10 years of age and vocabulary scores of the parents.

Domain (Test/Questionnaire)	Children born VPT Mean (SD)
Language (CELF-4)	**Standard scores**
Core Language index	89.4 (15.4)[1, 2]
Receptive Language index	89.2 (13.8)
Expressive Language index	90.0 (15.3)
Language Context index	89.9 (13.3)
Language Form index	89.3 (14.4)
Working Memory index	101.7 (13.4)
Vocabulary (PPVT-III)	**Standard scores**
Child's receptive vocabulary knowledge	98.7 (10.7)[2]
Intelligence (WISC-III)	**Standard scores**
Verbal IQ	95.9 (12.7)[1]
Performance IQ	89.4 (14.4)
Total IQ	92.0 (13.1)
Behavior (CBCL/TRF)	**T-scores Mean Mother/Father/Teacher**
Total problems	52.2 (9.0)
Internalizing problems	53.2 (9.0)
Externalizing problems	48.2 (8.1)
Social problems	56.0 (5.1)
Thought problems	55.9 (5.2)
Attention scale	58.0 (7.9)
Executive Functions (BRIEF)	**T-Score Mean Parents/Teacher**
Total	47.2 (8.5)
Behavior Regulation Index	46.9 (9.0)
Vocabulary (PPVT-III) of Parents	**Standard scores Mean (SD)**
Parent's receptive vocabulary knowledge (N=54)	93.9 (11.6)

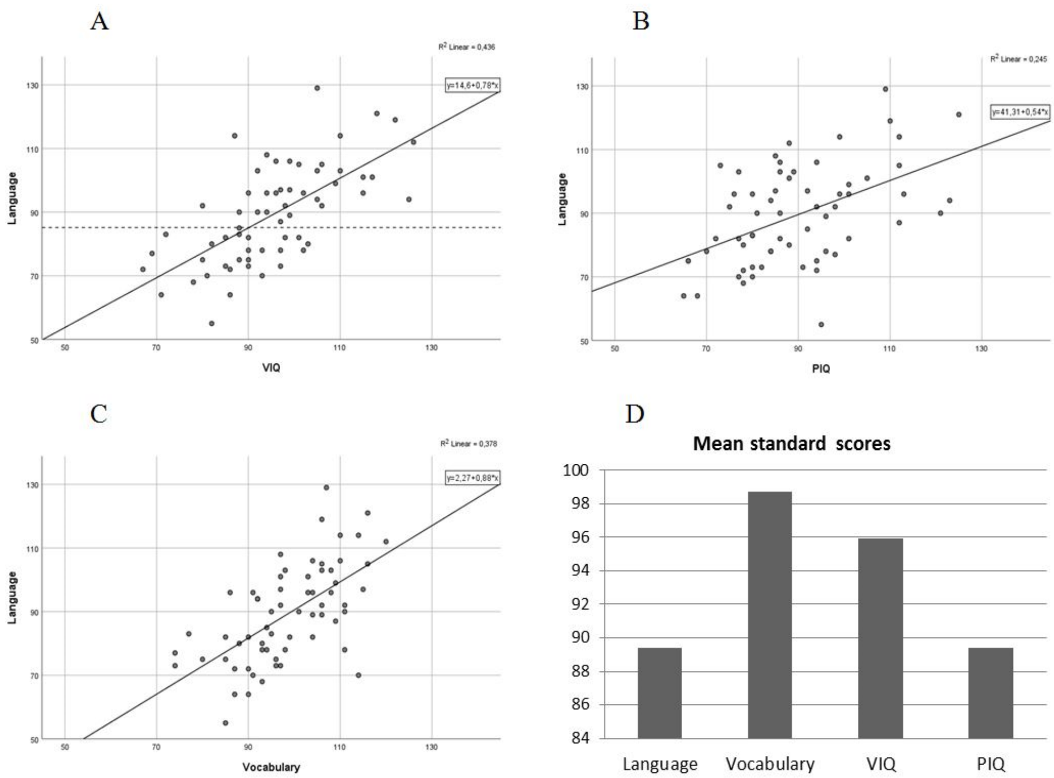
[1]Significant difference between Core language index and verbal IQ (mean difference=6.4, p<.001) .
[2]Significant difference between Core language index and child's receptive vocabulary knowledge (mean difference=9.3, p<.001).

Results

The baseline characteristics of the study group (n=63) did not significantly differ from the non-participating group (n=169) (Appendix). A Core Language Score below average (i.e. less than -1 SD) was assigned to 27 (43%) of the children, a significantly higher proportion than the 16% in the population of all children (Pearson's chi-square = 24, p<.01). Seven (11%) children had hearing thresholds of at least one ear above 30 dB, which means they had at least a mild hearing loss in at least one ear. The hearing problems were successfully rehabilitated with appropriate hearing aids. Consequently, the hearing ability of these seven children was sufficient and not likely to affect the language assessment.

The mean CL score was significantly lower than the mean vocabulary score (mean difference=9.3, p<.001). The standardized effect size of this difference was moderate to large (Cohen's d=.70, 95% C.I.=.34-1.06). The mean CL score was also significantly lower than the mean VIQ score (mean difference=6.4, p<.001). The standardized effect size of this difference was moderate (Cohen's d=0.48, 95% C.I.=.12-.83) (Fig 2, Table 1). A scatterplot of the correlations of language with VIQ, PIQ and vocabulary respectively are

Figure 2. Scatter plots with correlation fit of language scores with verbal IQ (VIQ) scores (A), performance IQ (PIQ) scores (B) and vocabulary scores (C) respectively and mean scores (N=63) of language, vocabulary, VIQ and PIQ. The dashed line in figure A represents language=85, which refers to a Core Language Score of 1 SD below the mean. Language scores <85 indicate the need of intervention in the clinical setting.



shown in Figure 2. At case level, almost three times as many children showed VIQ>language than VIQ<language. For the total study sample, there were no significant differences between mean scores on subtests and indexes of the CELF-4, except for Working Memory index. The mean score on the Working Memory index was significantly higher (i.e. more favorable) than the Core Language Score (mean difference=12.3, $p<.001$) (Table 1).

Multiple linear regression analysis showed that VIQ ($\beta=.649$ $p<.001$) and PIQ ($\beta=.260$ $p=.035$) were significantly associated with language outcome. Attention problems ($\beta=.137$ $p=.688$) and regulation problems ($\beta=-.155$ $p=.515$) were not significantly associated with language (Table 2). The total explained variance (R2) was .486.

The second multiple linear regression analysis indicated that number of days of assisted ventilation (β =-.592 $p=.015$) and mother's vocabulary score (β =.473, $p=.014$) were significant predictors for the child's language score: a longer period of assisted ventilation was related to lower language scores and better receptive vocabulary knowledge of the

Table 2. Multiple regression analysis with Core Language Score at 10 years of age as dependent variable. In regression analysis A perinatal and familial factors were included as independent variables (N=63). In regression analysis B neurodevelopmental child factors at 10 years of age were included as independent variables (N=54).

Regression analysis A: neurodevelopmental factors (N=63)						
	Unstandardized Coefficients		**Standardized Coefficients**		**95% Confidence Interval**	
	B	**Std. Error**	**Beta**	**Sig.**	**Lower bound**	**Upper bound**
(Constant)	3.455	23.426		.883	-43.473	50.383
VIQ	.649**	.139	.531	<.001	.215	.927
PIQ	.260*	.120	.241	.035	-.030	.501
Attention problems	.137	.339	.055	.688	-.619	.815
Regulation problems	-.155	.236	-.090	.515	-.820	.318

Regression analysis B: neonatal and familial factors (N=54)						
	Unstandardized Coefficients		**Standardized Coefficients**		**95% Confidence Interval**	
	B	**Std. Error**	**Beta**	**Sig.**	**Lower bound**	**Upper bound**
(Constant)	39.705	16.293		.019	6.890	72.521
Sex	5.582	4.024	.179	.172	-2.523	13.686
Mothers' education	.139	2.482	.008	.956	-4.861	5.139
Parent's vocabulary	.473*	.184	.361	.014	.102	.845
N days of assisted ventilation	-.592*	.233	-.352	.015	-1.061	-.122

mother was related to higher language scores. Sex (β =5.582, p=.172) and mother's educational level (β =.139, p=.956) were not significant predictors for language scores at 10 years of age (Table 2). The total explained variance (R2) was .522.

Discussion

In a group of 63 children born VPT of 10 years of age without major handicaps the mean VIQ and mean vocabulary score were significantly higher than their mean Core Language Score. For individual children in the clinical setting this means that VIQ and vocabulary knowledge may not reflect language difficulties directly and language problems can only be detected by extensive language assessment. The combination of the significant difference between the mean VIQ and mean language score and the significant positive association between VIQ and language scores may contribute to a more adequate identification of children born VPT at risk for language problems during clinical follow-up. Hence, children born VPT with a VIQ in the low average range (between 85 and 91) are at serious risk for language problems (i.e. Core Language Score <1SD, which indicates the need of intervention) and they should be assessed by a speech-language pathologist. However, there is a wide range of language scores for children with a VIQ score between approximately 91 and 105. It might therefore be desirable to assess the language functions of a wider range of children and add a speech-language pathologist to the multi-disciplinary team of follow-up of children born VP. These results add weight to the literature that showed the importance of language difficulties in children born VPT and the large number of children with below average language scores (5, 14, 22, 33-35).

Except for VIQ, PIQ was also significantly associated with language functions. Since the mean PIQ score was almost equal to the mean language score, this might lead to the idea that PIQ indicates language scores even better than VIQ. However, the correlation between PIQ and language scores was less strong (r=.507) than that of VIQ and language scores (r=.660). PIQ scores, therefore, do not provide a better indication of language scores than VIQ scores do. Although some studies associated attention and regulation problems with reading, spelling and oral language functions (24-26), we want to highlight our finding that attention and regulation problem scores did not seem to contribute to the diagnosis of children at risk for language problems in our sample.

Regarding our third objective, we determined the impact of several possible perinatal and familial risk factors on the child's language score. Significant predictors were number of days of assisted ventilation and the parent's vocabulary score. Surprisingly, parent's vocabulary knowledge was a better predictor than the child's sex and the mother's educational level, which are already well-known risk factors for overall long-term neurodevelopmental deficits in children born VPT (11). The distribution of the educational level of the mothers, unfortunately did not represent the distribution in the normal population, since our sample contained more higher educated parents. However, the distribution in our study sample, coincidentally did match the distribution of the norm reference group of the CELF-4-NL very well (N=873) (28), which is relevant since we compared our data to these norm references. We also want to emphasize that parent's vocabulary knowledge did not highly correlated with parent's educational level (r=.349), which indicates that parent's vocabulary knowledge may be a new, additional contributor to predicting language outcome.

The brain develops rapidly in the third trimester of pregnancy and early exposure to extra uterine life can impact brain development. Therefore, neuro-developmental difficulties in children born VPT have often been related to atypical brain development. Several neuroimaging studies in infants born VPT have shown atypical development of cortical and deep grey matter structures and altered connectivity of neural networks (36). The relatively low scores on complex language in the current study may also be associated with atypical brain development. It has been suggested that children born VPT have alternate pathways for language processing (37) and that they maintain atypical bilateral language organization much longer than term born controls (38). At the age of 10, children born VPT might not yet have a predominant left-sided language organization, which might explain their difficulties with complex language tasks. Besides, the systematic review of Stipdonk et al. (Chapter 3) showed the complex relations between structural brain measures and language related outcome measures in school-aged children born VP. Although it showed a predominant role for the corpus callosum, the cerebellum and uncinated fasciculus in relation to language functioning, future research is needed to study these relations in more detail, with in-vivo microstructural brain measures (such as diffusion MRI based tractography connectome reconstructions) in combination with adequate complex language measures (39).

Strengths and Limitations

A strength of this study is that children born VPT were extensively assessed with the complete test battery of CELF-4, the complete WISC-III, and behavior and executive functioning questionnaires. The limited sample size, however, prevented the inclusion of more predictors in our regression model. Another limitation were the missing values on the parent's vocabulary score. Therefore, the regression analysis on neonatal and familial factors was based on N=54. The relatively high educational level of the parents in our cohort might have also caused a bias. Our sample, therefore, might not be representative for children born VPT with lower educated parents.

Recommendations and future research

For future research it would be valuable and important to study the longitudinal trajectory of language functions to contribute to a better understanding of the atypical language development in children born VP. Differentiation between neurodevelopmental profiles at an early age and following their developmental trajectories might contribute to a better prediction of the complicated development of children born VP. Subsequently, the efficacy of speech-language interventions should be an important topic for future research as well. Besides, as emphasized earlier, it is crucial to study the associations between language difficulties and underlying brain structures and tracts in more detail. Lastly, we suggest that language functions be extensively assessed, rather than simply measuring vocabulary knowledge, especially when language is studied in school-aged children.

For clinical purposes, we recommend that clinicians of children born VPT assess language functioning in, at least, the children with a VIQ in the low average range (between 85 and 91). Since the mean Core Language Score was almost 10 points lower than the vocabulary score in this study, we suggest using language test batteries rather than vocabulary tasks, to avoid overestimating the verbal competencies in these children. According to the current clinical guidelines follow-up assessments are conducted only at 2 and 4 years of age (1, 2). However, we think that language functions are at least as important to assess at school age because of the increasing complexity of language use and the persistent or even increasing language problems throughout childhood. Therefore, it might be advisable to add, or more frequently request, the expertise of a speech-language pathologist to the multi-disciplinary team for the follow-up of children born VP. This recommendation adds to the suggestions of the recently published European Standards of Care for Newborn Health (40).

Conclusions

The language scores of the studied cohort of 10-year-old children born VPT without severe disabilities were significantly worse than their vocabulary scores and VIQ, while, at the same time, VIQ was strongly associated with language scores. These findings may contribute to more accurate diagnosis of language problems in school-aged children born VP, since most clinical guidelines for follow-up of children born VPT do not include language testing. It is important for clinicians following up children born VPT to realize that children with VIQ scores in the low average range are at risk for language problems, which may lead to academic and societal difficulties.

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Appendix

Study sample characteristics

Characteristics	**Study group (N=63) (%)**	**Non-participating group (N=169) (%)**
Gestational age, weeks, mean (SD)	29.0 (2.1)	29.3 (1.7)
Birthweight, grams, mean (SD)	1190 (407)	1217 (338)
Female sex	27 (43%)	80 (47%)
Neighborhood social economic status	-.04 (.97)	-.02 (.98)
Educational level mother, low to high	Unknown: 5 (8%)	-
1: High school	1: 11 (18%)	-
2: Intermediate vocational education	2: 21 (33%)	-
3: Higher vocational education	3: 20 (31%)	-
4: University level	4: 6 (10%)	-
Age (years;months) at assessment, mean (SD)	10;6 (0;7)	-
ADHD diagnosis (parent-reported)	10 (16%)	-
Left-handed (parent-reported)	14 (22%)	-
Hearing threshold of one ear above 30 dB – wearing hearing aids	5 (8%) – 3 (5%)	-
Hearing threshold of both ears above 30 dB – wearing hearing aids	2 (3%) – 2 (3%)	-
Special school services	7 (11%)	-
Received speech-language therapy in past	33 (52%)	-
Language score above 85	36 (57%)	-
Of which received speech-language therapy	13/36 (36%)	-
Language below 85	27 (43%)	-
Of which received speech-language therapy	20/27 (74%)	-
Language below 70	4 (6.3%)	-
Of which received speech-language therapy	4/4 (100%)	-

Differences between the study group and non-participating group were calculated with independent t-test or Pearson's chi-square test and were not significant ($p>.05$).

Language functions deserve more attention in follow-up of

Language and brain structures in preterm children: A systematic review

Neurodevelopmental profiles preterms

Auditory maturation preterm

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

Lateralization in very preterm children

Narrative retelling in preterm born children.

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Chapter 5

Does a narrative retelling task improve the assessment of language proficiency in school-aged children born very preterm?

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Jeroen Dudink

Irwin Reiss

Marie-Christine Franken

Clinical linguistics and phonetics, 2020

ABSTRACT

Background

Almost half of children born very preterm (VPT) experience language difficulties at school-age, specifically with more complex language tasks. Narrative retelling is such a task. Therefore, we explored the value of narrative retelling assessment in school-aged children born VP, compared to item-based language assessment.

Method

In 63 children born VPT and 30 age-matched full-term (FT) controls Renfrew's Bus Story Test and Clinical Evaluation of Language Fundamentals were assessed. The retelling of the Bus Story was transcribed and language complexity and content measures were analyzed with Computerised Language Analysis software.

Results

Narrative outcomes of the VPT group were worse than that of the FT group. Group differences were significant for the language complexity measures, but not for the language content measures. However, the mean narrative composite score of the VPT group was significantly better than their mean item-based language score, while in the FT group the narrative score was worse than the item-based score. Significant positive correlations between narrative and item-based language scores were found only in the VPT group.

Conclusions

In conclusion, in VPT children narrative retelling appears to be less sensitive to detecting academic language problems than item-based language assessment. This might be related to the mediating role of attention in item-based tasks, that appears not to affect more spontaneous language tasks such as retelling. Therefore, in school-aged children born VPT we recommend using narrative assessment, in addition to item-based assessments, because it is more related to spontaneous language and less sensitive to attention problems.

Introduction

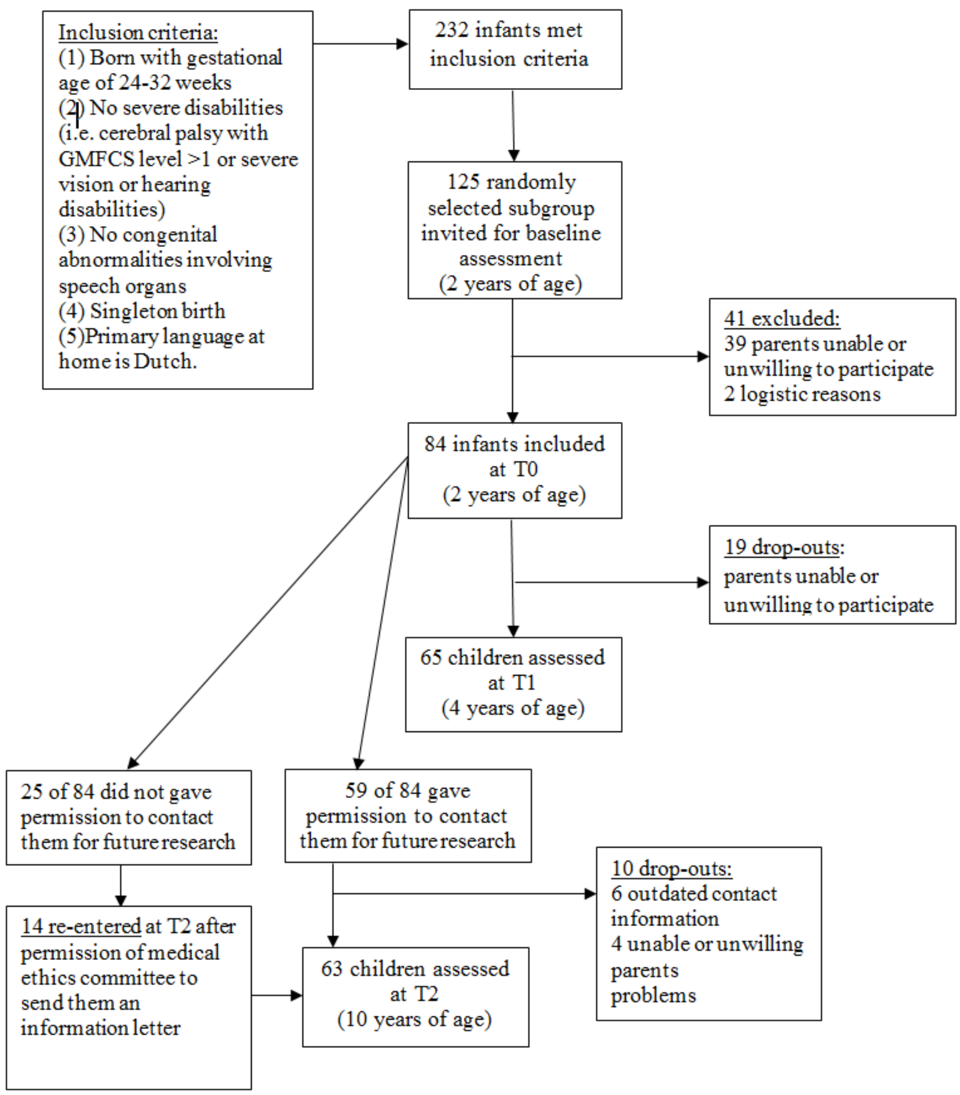
Nowadays, children born very preterm (VPT, <32 weeks) represent 1%-2% of all live births in developed countries (1). Since the survival rates of infants born VPT have improved over the last decades, the number of children with neurodevelopmental problems during childhood has increased (2). Approximately 40% of children born VPT without major handicaps have neurodevelopmental disabilities at school age such as learning, behavioural and language problems (3-8). Regarding language, it has been shown that children born VPT experience problems with more complex language tasks and to a lesser extent with simpler language tasks such as a receptive vocabulary test (4, 9).

Complex language assessments

Complex language tasks require integration of multiple language components. Usually, an overall complex language score is assessed with a standardised item-based test battery such as the Clinical Evaluation of Language Fundamentals-4 (CELF-4) (10). This item-based language test battery is based on the sum of subtests, each assessing a specific task such as recalling sentences, following directions or formulating sentences. Each language subtest represents one or a few language competency, such as vocabulary, morphology or syntax. However, there is not one single subtest integrating all language components into an overall language performance outcome. Narratives, on the other hand, are not based on discrete skill testing, but require integration of various cognitive, linguistic and social skills (11). Therefore, narrative ability can be assumed to represent spontaneous language performance. It has been described as one of the most "ecologically valid ways" in which to measure communicative competence, both in normal populations and in clinical groups (12, 13). A narrative assessment represents the telling or retelling of a fictional or factual story. It provides rich information about linguistic microstructures (e.g. vocabulary, morphology and syntax) as well as macrostructures (such as the organization of events in the plot and coherence in the story) (14). For clinicians, assessing the child's ability to narrate may be useful since this task may contribute to evaluating how the child's daily communication is affected, and give direction for language therapy (12). Besides, the same authors suggest that relatively subtle language difficulties can be detected on the basis of narratives. Since language difficulties of children born VPT vary widely, narrative assessment might be specifically useful to this patient group. In comparison with other discourse-level language, such as conversation and free-play, a narrative retelling task requires language use in a specific context and structure and it elicits more complex syntactic structures (15-18). The Bus Story Test is a narrative retelling assessment tool that contains the most recent norm-references for Dutch school-aged children (11, 14). Performance on the Bus Story is supposed to be predictive of future language and literacy performance (19).

To our knowledge, so far only two studies used a narrative task in children born VP. Crosbie et al. assessed the Bus Story Test in 15 ten-year old children born VPT and 15 full-term (FT) peers, and showed children born VPT to have more utterances with mazes and more disruptions (20). However, the children born VPT produced a similar story compared to that of their FT peers in terms of content, structure, length of story and complexity. There were neither any group differences on most of the standardised measures on the CELF-4 subtests, Wechsler Intelligence Scale for Children-IV (WISC-IV) and British Picture Vocabulary Scales-II (BPVS-II) (20). Smith et al. compared 28 VPT born twin pairs to 28 FT born twin pairs at ten years of age and assessed the Test of Narrative Language (TNL) in combination with four subtests of the CELF-4 (21). The VPT twin group performed

Figure 1. Flow-chart of inclusion process of the cohort.



significantly worse on the item-based standardised tests, but, unexpectedly, not on the narrative assessment. The authors encouraged other researchers to evaluate discourse-level language studies among children born VPT and also to look into the influence of attention on standardised test performances.

The recently published European Standards of Care for Newborn Health (EFCNI) (22) recommended the assessment of language problems not only in the first years of life, but also at school-age. However, there is not yet any evidence-based protocol for the assessment of complex language skills in school-age children born VP. Hence, more research is needed to ascertain how to assess complex language functions in school-aged children born VP. Narrative retelling may refer to spontaneous language performance, required for daily conversations, while item-based language scores might refer to more academic language use. A study that compares in more detail narrative retelling in a sample of VPT and FT singleton children with standardised item-based language assessments, would contribute to diagnosing language difficulties in children born VPT more adequately.

Aims

Therefore, the aim of this study is to explore the added value of assessing narrative retelling ability in school-aged children born VP, compared to item-based language assessment. In other words; does narrative retelling ability provide unique information about the language proficiency in school-aged VPT children? We expected children born VPT to have worse narrative ability than their FT born peers. Besides, we hypothesized that narrative measures of children born VPT as well as FT would be associated with their standardised language test scores. However, we also hypothesised that children born VPT would score worse on a narrative assessment than on an item-based language assessment.

Materials and method

Participants

This study was part of a longitudinal cohort study into speech, language and brain development in children born VP. The children had been admitted to the NICU 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). Parents of participants have given written informed consent for participation and publication. The study inclusion flow-chart is presented in figure 1. The present study concerns 63 children born VP, at age 10 years (T2). Inclusion criteria were: (1) Born with gestational age of 24-32 weeks; (2) No severe disabilities (i.e. cerebral palsy with GMFCS level >1 or severe vision or hearing disabilities); (3) No congenital abnormalities involving speech organs; (4)

Singleton birth; (5) Primary language at home is Dutch. As a cross-sectional control group, 30 FT born children, matched on age and sex, were assessed.

Procedure and Materials

The Core Language Score of the CELF, the Renfrew Bus Story Test and hearing thresholds were assessed during a one-day visit to Erasmus-MC Sophia's Children's Hospital for both children born VPT and FT. In addition, parents of the FT born participants completed a questionnaire requesting: the exact gestational age and birth weight; whether there had been pregnancy or neonatal complications; the educational level of the mother (based on the Dutch educational system); handedness of the child; whether the child had been diagnosed with other disorders (such as ADHD and dyslexia); whether the child had been treated for speech or language difficulties and for how long. This information was already available for the children born VP, since they were being followed longitudinally.

As hearing functioning can affect oral language functions directly, hearing thresholds were measured to detect any hearing losses. A certified clinician according to the ISO standard 8253-1(23) performed pure-tone audiometry (0.5, 1, 2 kHz) and tympanometry in a soundproof booth. A computer-based clinical audiometry system (Decos Technology Group, version 210.2.6 with AudioNigma interface) and TDH-39 headphones were used.

Clinical Evaluation of Language Fundamentals, Fourth Edition (CELF-4), validated and normed for Dutch children (10), is an instrument used to detect language and communication disorders in children of 5-18 years of age (24). The CELF-4 consists of 11 language subtests. The Core Language Score is the mean score of five of these subtests (i.e. Concepts & Following Directions; Recalling Sentences; Formulating Sentences; Word Classes Receptive and Word Classes Expressive), providing a general language proficiency index. It was administered by a certified speech-language pathologist. Based on a normally distributed scale, the mean standard score for each subtest is 10, and the standard deviation (SD) is 3. The Core Language Score is also normally distributed, however, with a mean of 100 and an SD of 15. Norm references were also converted to z-scores.

The Renfrew Bus Story Test, validated and normed for Dutch children (14), is an instrument for assessing narrative retelling performance (25). Its assessment comprises the retelling of a story about a bus, supported with pictures representing the story, after the story has been read aloud by the examiner in the exact version that is written in the test manual. It was administered by a certified speech-language pathologist. The child's retelling was audio-recorded and transcribed and coded by one of three speech-language pathologists using CHAT (26). Based on these transcriptions, the following outcome measures were determined:

- Information score: The information score indicates the extent to which the child repeated the content of the story correctly.
- Mean Length of Utterances (MLU): The MLU reflects the length of the terminable unit, or T-unit, which refers to a main clause with any subordinate clauses. The MLU provides an index for syntactic development (15, 27).
- Mean Length of 5 Longest Utterances (ML5LU); The ML5LU provides an index of the complexity of the child's grammatical structures and it represents the maximum language capacity of children better than MLU and is less sensitive to some of the strategies employed to narrate stories, such as using many short sentences (28, 29).
- Number of Embedded Utterances (EU): The number of EU indicates clausal density, which is the average number of clauses (main or subordinate) per T-unit and provides an index of the complexity of the child's grammatical structures (15).
- Number of Ungrammatical Utterances (UU): The number of UU indicates the correctness of utterances and nuances language complexity measures (30)
- Vocabulary Diversity (VOCD): The VOCD is based on morphological codes of Computerised Language Analysis software CLAN(MacWhinney, 2000). It provides an index of the semantic diversity of the child's language use. In contrast to type-token ratio, VOCD is not impacted by sample size, since it is calculated based on a series of random text samplings. Higher values indicate greater diversity (31).

Dutch norm references are available for ML5LU, information score and number of EU of the Bus Story Test for children aged 4 to 10 years. Standard scores were also presented as percentile scores, which we also converted to z-scores. Furthermore, a composite z-score for narrative retelling was calculated, based on the z-scores of these three measures. This overall narrative retelling z-score could be used to compare the score on narrative retelling to the overall item-based language score of the CELF-4.

Reliability

To determine the interrater reliability, one of the three speech-language pathologists also transcribed and analyzed 20% of the samples that had been transcribed by the other two speech-language pathologists. Intraclass correlation coefficient (ICC) (26) and 95% confidence intervals were calculated over the individual scores on the six variables mentioned above.A two-way mixed effects model was used. Between speech-language pathologist 1 and 2 the ICC ranged from .980 to .994 and between speech-language pathologist 1 and 3 the ICC ranged from .984 to .998, which indicates an excellent interrater reliability (32).

Statistics

The statistical analyses were performed using IBM SPSS Statistics version 25. Pearson's chi-square test and independent t-test were used to compare the VPT children that participated in the present study (n=63) to the non-participating VPT children of the original cohort (n=169, from total n=232). Differences on gestational age, birth weight, sex and neighbourhood social economic status were tested. One-way ANOVA and ANCOVA were used to determine the difference between VPT and FT children on the narrative measures (information score; MLU; ML5LU; number of EU; number of UU; VOCD; narrative composite score) and the Core Language Score of the CELF, controlled for educational level of the mother, age and sex. A paired samples t-test was used to compare mean scores on narrative outcomes to mean Core Language Score for both VPT and FT children. The difference between the FT and VPT group on the narrative and item-based language difference was measured with ANOVA and ANCOVA. The correlations between the narrative measures and the standardised language scores were measured with Pearson's correlation coefficients. Differences between the correlation coefficients of the VPT and FT group were calculated with Fisher's r to z analysis.

Results

Group characteristics

Gestational age, birth weight, sex and neighborhood social economic status of the study group of children born VPT (n=63) did not significantly differ from the non-participating VPT children of the original cohort (n=169) (p>.05; table 1). Differences between the VPT and FT study groups in age at assessment, sex and neighborhood social economic status were also nonsignificant (p>.05). However, the difference in educational level of the mother between VPT and FT children approached the level of significance (p=.051).

Narrative scores: VPT vs FT group

Mean scores and SD's on narrative measures of the VPT and FT group and the mean differences between the groups are presented in Table 2. When controlled for educational level of the mother, age and sex, the VPT group scored significantly worse on the narrative composite score (p=.021), the ML5LU (p=.012), the number of EU (p=.049) and the item-based language score of the CELF (p<.000) than the FT group, based on an ANCOVA. Since educational level of the mother was missing for five patients, the ANCOVA was based on a patient group of 58. However, ANCOVA results did not differ from ANOVA results based on all 63 patients. The effect sizes were small to moderate for the narrative measures and large for the Core Language Score of the CELF. No group differences were found on the information score (p=.179), number of UU (p=.220) nor VOCD (p=.311).

Narrative versus item-based language measures

In the VPT group the mean composite z-score of the narrative assessment was significantly higher than the mean item-based language z-score of the CELF (p=.016). Conversely, in the FT group the mean narrative composite z-score was lower than their item-based language z-score, although this difference did not reach the level of significance (p=.115; Figure 2). Consequently, the VPT and FT group differed significantly on the difference score

Table 1. Study sample characteristics.

Characteristics	Very preterm (n=63)	Non-participating Very preterm (n=169)	Full term (n=30)
Gestational age in weeks, mean (SD)	29.0 (2.1)	29.3 (1.7)	39.6 (1.3)
Birth weight in grams, mean (SD)	1190 (407)	1217 (338)	3469.1 (450)
Female sex, N (%)	27 (43%)	80 (47%)	11 (37%)
Neighborhood social economic status, mean (SD)	-.04 (.97)	-.02 (.98)	.20 (.82)
Age (years;months) at assessment, mean (SD)	10;6 (0;7)	-	10;3 (0;11)
ADHD diagnosis, N (%)	10 (16%)	-	3 (10%)
Left-handed, N (%)	14 (22%)	-	1 (3%)
Special school services, N (%)	7 (11%)	-	0
Educational level mother, low to high, N (%)	Unknown: 5 (8%)	-	
1: High school	1: 9 (14%)		1: 3 (10%)
2: Secondary vocational education	2: 23 (36%)		2: 5 (17%)
3: Higher vocational education	3: 20 (32%)		3:19 (47%)
4: University level	4: 6 (10%)		4: 10 (26%)
Hearing threshold of one ear above 30 dB – wearing hearing aids	5 (8%) – 3 (5%)	-	0
Hearing threshold of both ears above 30 dB – wearing hearing aids	2 (3%) – 2 (3%)		0
Received speech-language therapy in past	33 (52%)	-	8 (26%)

Table 2. Mean standard scores of narrative measures and Core Language Score of CELF and the composite narrative z-score for VPT and FT groups and the effect of group on these measures, based on a one-way ANCOVA, controlled for educational level of the mother, age and sex. Standardised mean-difference effect size (d) was calculated based on means, standard deviations and sample sizes.

ANCOVA	Very preterm n=58		Full term n=30				
					ANCOVA Effect of group		
	Mean	SD	Mean	SD	F	p-value	Effect size (d)
Narrative Composite score	-.37	.86	.04	.64	6.0	.016	.52
Information score	21.5	5.0	22.6	5.0	1.8	.179	.22
ML5LU (in words)	11.7	2.3	12.9	1.8	6.6	.012	.56
Number of Embedded Utterances	3.7	2.3	4.6	2.3	4.0	.049	.39
Number of Ungrammatical Utterances	2.5	1.7	2.0	1.5	1.7	.202	.30
VOCD	37.3	8.2	39.2	6.6	1.0	.311	.25
Core score CELF	89.8	15.7	105.1	11.5	18.1	.000	1.06

Table 3. Effect of group in differences on the narrative-language difference of each group, based on ANOVA and ANCOVA, controlled for educational level of the mother, age and sex. Standardised mean-difference effect size (d) is calculated based on means, standard deviations and sample sizes.

ANOVA							
Difference score VP (n=63)		**Difference score FT (n=30)**					
Mean	SD	Mean	SD	Mean diff	95% confidence interval	p-value ANOVA	Effect size (d)
.31	1.0	-.31	1.0	.62	.20 to 1.09	.007	.62
ANCOVA							
Difference score VP n=58		**Difference score FT n=30**		**ANCOVA (N=58)**			
Mean	SD	Mean	SD	**F**	p-value		
.31	1.1	-.31	1.0	3.9	.051		

Table 4. Number of children scoring above and below -1 SD (i.e. "average" and "below average") on composite narrative score and Core Language Score CELF in VPT and FT group.

	Below Average Core Language Score CELF	**Average Core Language Score CELF**	**Total**
Below Average Composite narrative score	VP: 13 (20%) FT: 0	VP: 6 (10%) FT: 2 (7%)	VP: 18 (29%) FT: 2 (7%)
Average Composite narrative score	VP: 15 (24%) FT: 1 (3%)	VP: 29 (46%) FT: 27 (90%)	VP: 44 (71%) FT: 27 (93%)
Total	VP: 27 (44%) FT: 1 (3%)	VP: 35 (56%) FT: 29 (97%)	VP: 63 (100%) FT: 30 (100%)

Figure 2. Mean Z-scores for Core Language Score of the CELF and composite score of narrative retelling of Bus-story for VPT and FT group.

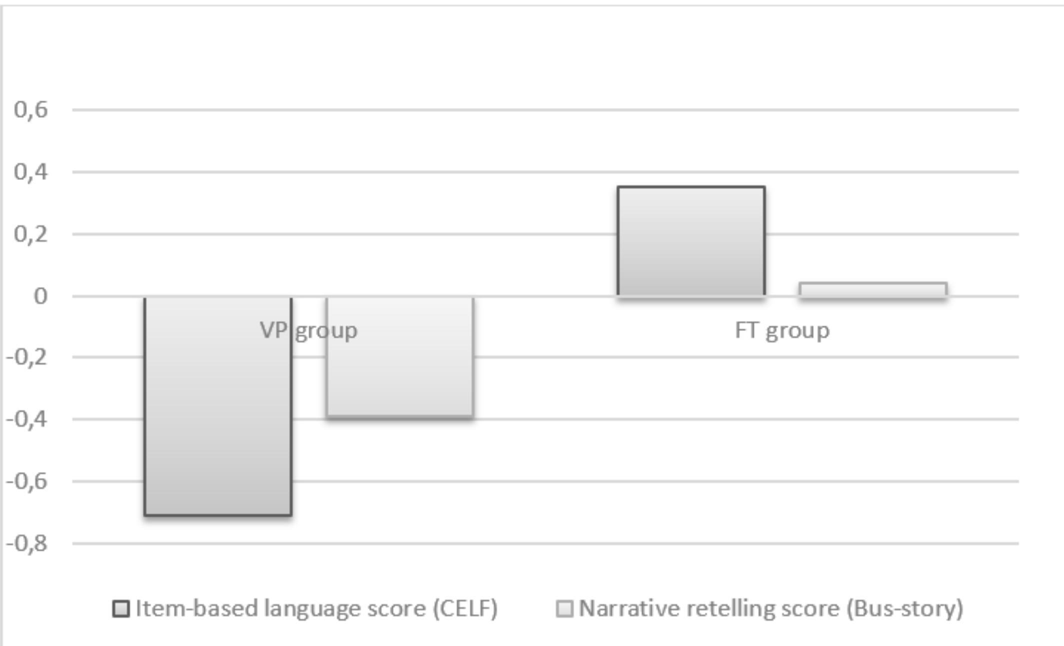
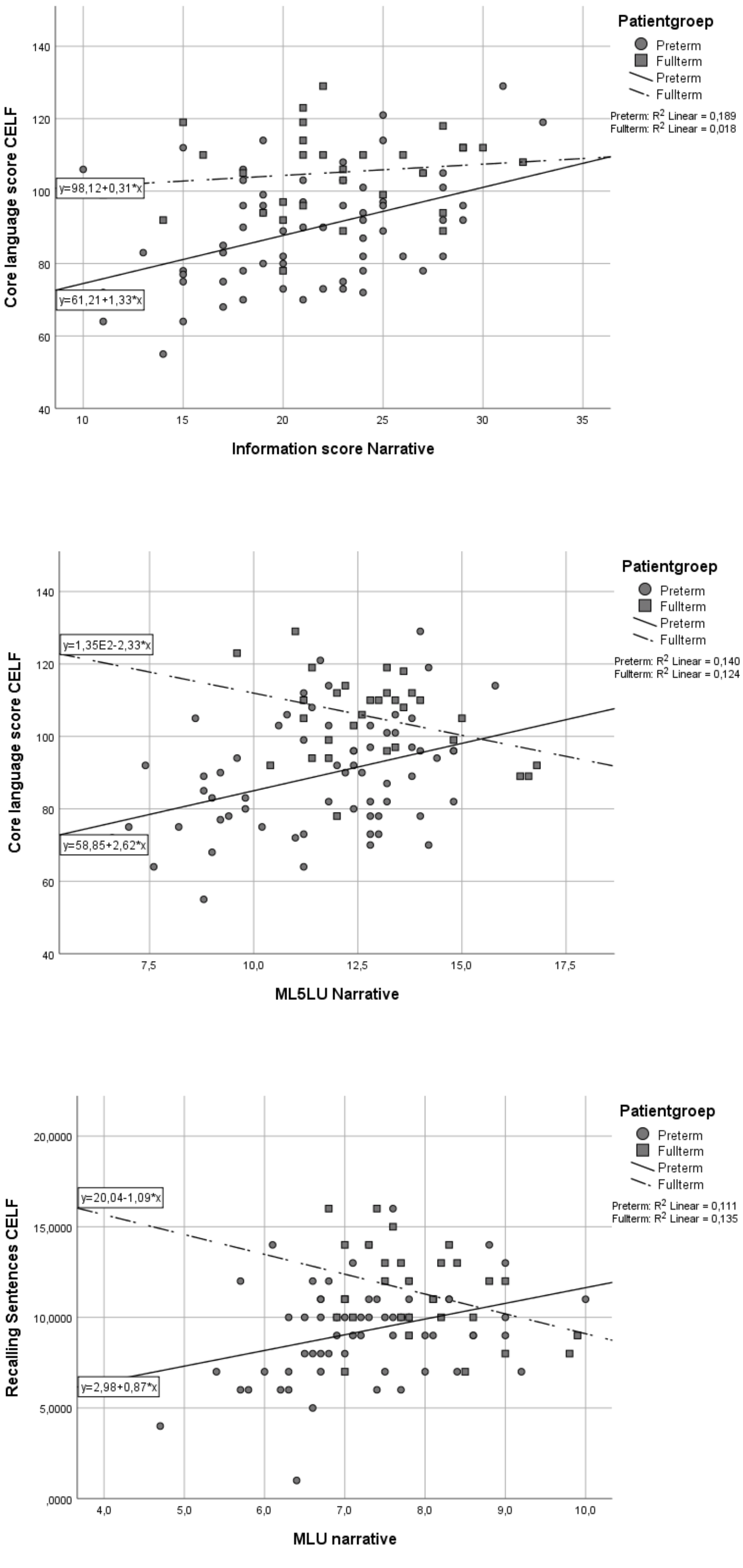


Figure 3. Scatterplots and linear fit lines of VPT en FT group.



between the composite narrative score and item-based language score (p=.007, effect size=.62). However, after controlling for educational level of the mother, age and sex, the p-value of this effect of group (i.e. VPT or FT) was p=.051 (Table 3). In addition, the number of children born VPT with below average scores (i.e. < -1 SD below the mean of the norm reference group) on the item-based language score of the CELF, in combination with average scores on the narrative composite score was significantly higher (n=15, 24%) than the number of FT children with this combination of scores (n=1, 3%; table 4).

Association measures

All correlations between subtests and item-based language scores of the CELF narrative measures are presented in the Appendix. Scatterplots of the significant associations between narrative and item-based language measures are presented in Figure 3. In the VPT group, a significant positive correlation between the item-based language score of the CELF and the narrative information score was found (r=.435, p<.001), which was not found in the FT group (r=.135, p=.477). Based on Fisher's r to z transformation, these correlation coefficients of the VPT and FT group were not statistically significant (z=1.425, p=.154). Between the item-based language score and ML5LU a significant positive correlation was found in the VPT group (r=.374, p=.003), while in the FT group a negative correlation was found, which, however, did not reach the level of significance (r= -.353, p=.056). Comparing these correlations, a significant difference was found (z=3.288, p=.001). The difference between groups on the correlation between the subtest score on Recalling Sentences of the CELF and the MLU score of the narrative retelling task was also significant (z=3.131, p=.002); the VPT group showed a significant positive association (r =.327, p=.009), while the FT group showed a significant negative association (r= -.368, p=.046).

Discussion

Although children born VPT without major handicaps score worse on narrative retelling than FT peers, their narrative ability was significantly better than their item-based language skills. FT children, conversely, had worse narrative ability compared to their standardised language skills. More than a quarter of the VPT group showed sufficient narrative ability, but below average scores on an item-based language test. Therefore, our hypothesis (assuming that children born VPT experience more problems with narrative retelling than with item-based language assessments since it is technically a more complex task) has to be rejected. Our findings suggest that children born VPT have fewer problems with the spontaneous use of language in a narrative retelling task than with the abstract assessment of isolated language skills. Narrative retelling assessment therefore appears to be less sensitive than assessment of standardised isolated complex language skills in detecting the more academic language difficulties in children born VP. However, the specific associations between narrative measures and item-based language measures that were found only in children born VPT showed the added value of narrative retelling assessment in defining and specifying language difficulties in this patient group. Narratives provide detailed information about the type of language difficulties and coping strategies of children born VP. In our group of children born FT, on the other hand, narrative ability was relatively weak. This suggests that language interventions for FT children with language difficulties might need to be more focused on narrative ability than on isolated language skills.

Interpretation and meaning of results

An explanation for the better narrative performance of children born VPT might be found in the nature of narratives. Since a narrative is a relatively natural language task, representing the spontaneous use of language more adequately than abstract subtests of an item-based language test, children born VPT might experience less difficulties with it.

This difference between tasks might be impacted by the required level of sustained attention in each task (33). It is well-known that children born VPT have more attention problems than FT born peers (34, 35). The duration of an item-based language assessment is much longer than that of a narrative retelling assessment, resulting in different levels of sustained attention. Besides, the Bus Story Test is supported with pictures, which might make it easier to concentrate on the task, compared to the numerous items and turn-taking shifts that are required in an item-based language assessment. Thus, a narrative retelling assessment requires less sustained attention than an item-based language assessment. Note that spontaneous narrative telling requires even less sustained attention than a retelling assessment. Following this reasoning, item-based language assessment might overestimate language problems in children with attention problems. In these children, item-based language scores may predominantly reflect academic language functions rather than spontaneous language proficiency. Future research will be needed to explore this idea. Nevertheless, a narrative task may be a valuable addition to item-based language tests, as a task that is more strongly related to spontaneous speech and less sensitive to attention. Consequently, narrative assessment may improve diagnosis of language difficulties in children born VP.

Furthermore, the relatively good performance on narrative retelling might also be associated with the relatively high vocabulary scores of this group (4, 9). Stipdonk et al. showed in the same study group that mean vocabulary scores were significantly higher than mean scores on the CELF-4-NL (9). Since narrative retelling ability, in general, is related to vocabulary knowledge, this might be an important association in children born VP.

A more fundamental explanation for our findings might be the atypical language tracts/ pathways in the brain of children born VP. Recently, Bruckert et al. found associations between reading ability and white matter pathways in children born FT, but not in children born VP, which suggested that children born VPT might have a larger, but less specific network of white matter pathways involved in reading (36). If the atypical brain development of children born VPT is indeed characterised by a more dispersed network without specifically good language subtracts, this might also explain their weak performance on isolated, specific language tasks and their relatively good performance on, more natural and free, language tasks.

Clinical Implications

For clinical purposes, we recommend using narrative retelling assessment, in combination with an attention task or questionnaire and item-based language tasks, in school-aged children born VP. Since retelling and item-based language functioning differed significantly in our VPT group, and both skills are needed for adequate language performance, it is relevant to assess both in clinical practice. In combination with attention skill assessment, narrative retelling will be relevant and complementary to item-based standardised language assessment in this patient group.

Narratives in children born VPT and FT: agreement with the literature

Although narrative performance of the VPT group was better than their isolated language skills, most of the narrative outcomes were still significantly worse than those of age-matched FT born peers. Specifically, the VPT group scored worse than the FT group on measures of the grammatical complexity of their story (i.e. ML5LU and number of EU), but not on content measures (i.e. information score and VOCD). This suggests that children born VPT experience more difficulty with using complex grammatical structures in a story than with applying more complex semantics. This result is not entirely in agreement with the results of Crosbie et al. and Smith et al. who also assessed narratives in children born VPT (20, 21). Neither of these studies found any differences between children born VPT and FT in the content or complexity of their stories. However, in both studies the VPT group did score significantly worse than the FT group on the subtests of the CELF, which is in accordance with the present study. Since Crosbie et al. studied a relatively small sample size (15 VPT and 15 FT children) and Smith et al. studied only twins, we think the present study adds to the literature.It leads to growing evidence that children born VPT with attention problems, may have fewer problems with retelling than with item-based language testing.

Associations between narrative and item-based language measures

The positive correlations between narrative measures (Bus Story's ML5LU and Information score) and the Core Language Score of the CELF in the VPT group, may reflect that children born VPT with better language scores use relatively lengthy sentences. This language style might match a low score on one of the five dimensions of language fluency, defined by Fillmore (1979) as "succinctness, the ability to speak in logically organised and semantically dense sentences such that ideas are expressed in a compact and careful way" (37). In children born FT, on the other hand, the narrative and item-based language scores were independent of the length or complexity of their utterances. Even negative associations were found, suggesting that better standardised language functions were associated with the use of shorter sentences in retelling for children born FT. This is the opposite relationship of that in children born VP. The causality of the relation in the VPT group remains unclear, however. In children born VP, there might be a common neurological cause for their language difficulties. As described in the previous paragraph, children born VPT might have a more dispersed language network in the brain, which might cause problems with isolated language skills and narrative ability. Another explanation of the significant association might be that language functions of children born VPT are influenced by their talking experience, and that externalising talkers develop better language skills than internalising talkers. A third possibility is that children born VPT with better language skills feel an urge to perform, and therefore use longer and more complex sentences than children born VPT with weaker language skills. More research and longitudinal studies with detailed linguistic analyses are needed to improve our understanding of these associations. Furthermore, it would be interesting to study in more detail the macrostructures of narratives in children born VP.

Strengths and Limitations

The strength of this study is that children born VPT and age-matched controls were linguistically analyzed in detail; item-based language assessments were performed and transcripts of a narrative retelling task were analyzed. Although analysis of narratives is time-consuming, we studied a relatively big sample with sufficient statistical power. Since the existing literature about language development in children born VPT is mainly based on item-based language assessments, this study adds to what was already known on this topic. Our sample seems to be representative for school-aged children born VPT without major handicaps, since our sample did not significantly differ from the non-participating group of VPT children of our cohort on gestational age, birthweight, sex and social economic status. Yet, our results cannot be generalised for children born late preterm or for other age groups. A limitation of the present study is that the VPT and FT group differed significantly on the educational level of the mother. We therefore controlled for this factor in all relevant analyses, together with age and sex. Another possible limitation of this study is that the children born FT might have been less motivated for the assessment than the children born VP. The children born VPT were the subject of the study and originally hospital patients, who were assessed for clinical reasons in the past. Therefore, they might have felt more pressure to perform well than the FT children who had no relation to the hospital at all. However, we do not know whether this difference in clinical record has impacted their test motivation and results. If they have been underperforming, this would mean that their actual narrative ability would be better, which would make the differences with the VPT group even bigger. In addition, we think it is improbable that the motivation for the narrative assessment was different from that of the item-based language assessment. Therefore, it appears unlikely that the results on association measures were impacted by their motivation. Another limitation of the study is that the norm references of the Renfrew Bus Story Test are based on children up to 10;0 years of age and that these norm references are relatively old (i.e. standardization studies took place between 2006 and 2013) (14). The mean age of the children of our study group was 10;6, with a minimum age of 9;0 and a maximum age of 12;0. All children are compared to the norm group of children aged 9;0-10;0. Since we were specifically interested in the differences between our VPT and FT group, we do not think this impacted our study results significantly. Besides, it was expected, based on the stabilization of scores of the norm references at 9-10 years of age, that narrative functions no longer develop quickly the age of 10(Jansonius, et al., 2014). However, if it would have impacted our results, the number of children scoring below 1 SD would have been bigger, suggesting that the actual narrative retelling performance of children born VPT and FT is worse.

Conclusions

The narrative retelling ability of children born VPT is relatively good compared to their standardised language scores, suggesting that children born VPT experience fewer problems with language tasks that are more strongly related to the spontaneous use of language, than with item-based assessments of isolated complex language skills. This difference between language tasks might be mediated by attention skills, suggesting that item-based language assessments sometimes overestimate spontaneous language functions in school-aged children born VP. Besides, children born VPT with higher language scores tended to produce longer utterances, while the language scores of FT children were independent of their retelling skills. Thus, narrative retelling assessment appears not to be more sensitive to language difficulties than item-based, standardised language tests, but it provides detailed information about the type of language difficulties and coping strategies of children born VPT and it may be a more attention-independent language assessment. Adding narrative retelling assessment to item-based standardised language assessments in school-aged children born VPT is, therefore, recommended.

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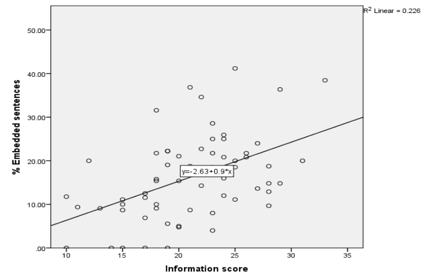
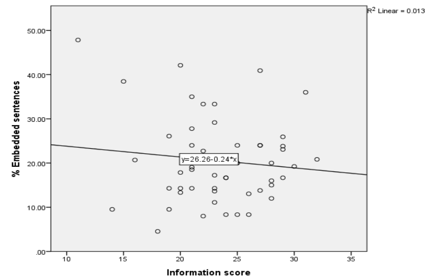
Appendix

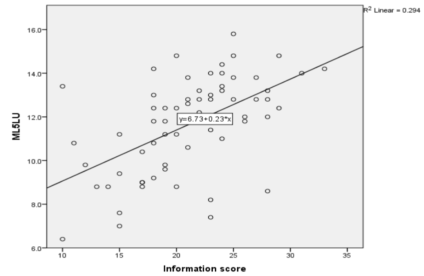
Scatter plots of item based language scores and narrative measures

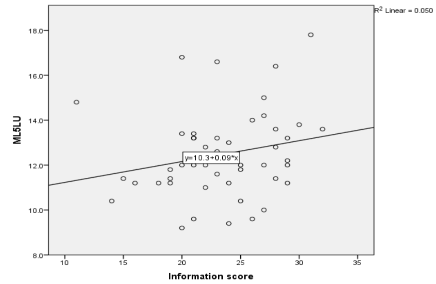
Very preterm children

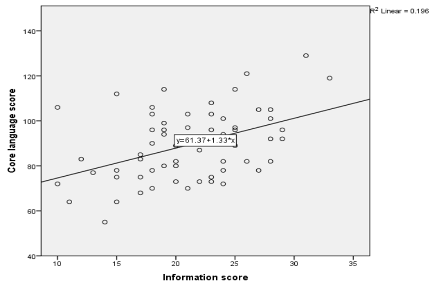
Full term children

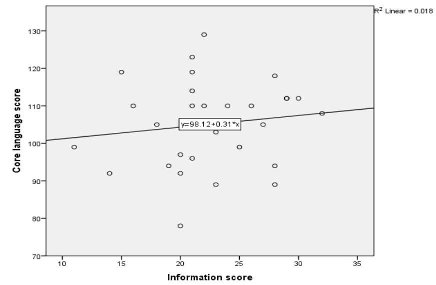


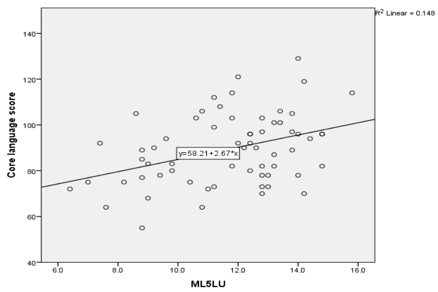


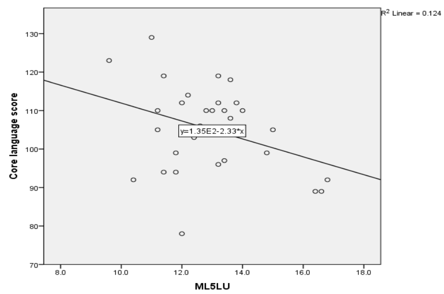












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Chapter 6

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

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Pediatric Research, 2021

ABSTRACT

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.

Objective

To ascertain whether total cerebellar structures or specific posterior lobular structures are associated with language ability of school-aged VPT children.

Method

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 grey matter (GM) cerebellar volume and right CrusI+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 (β=.192 (CI=.033, .351), p=.020).

Conclusion

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.

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 grey matter (GM) and white matter (WM) volumes than full term children (9). However, the relation between language and brain structures in children born VPT is complex, as both macro- 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 last 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).

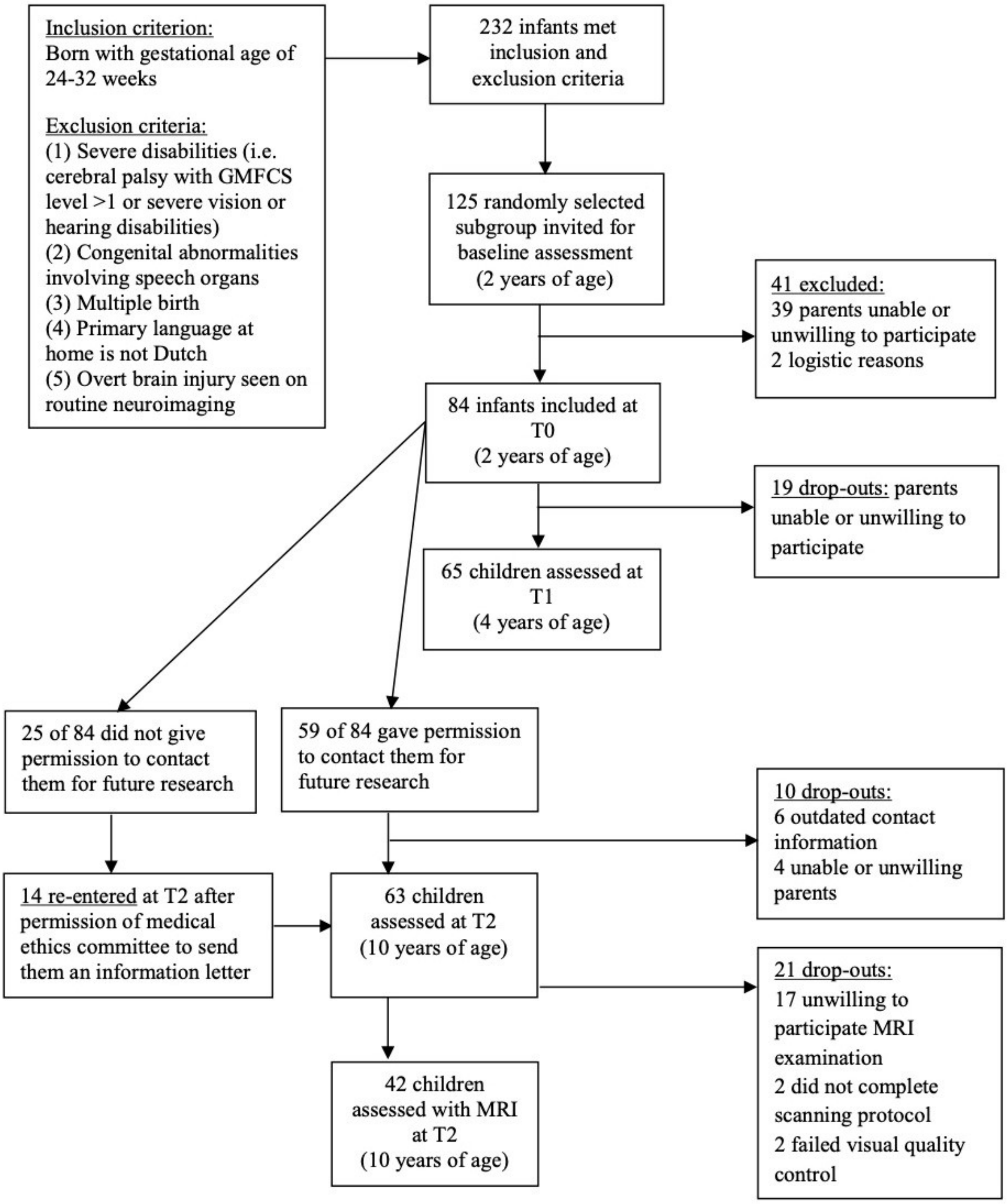
When it comes to language functions specifically, associations have been found between cerebellar damage and atypical language functions in both children and adults (24, 25). However, without overt cerebellar damage, the relation between the cerebellum and language functions appears to be more subtle. In volumetric studies, a positive relationship 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, 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 which 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 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, since 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 langue 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 full term 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,

Figure 1. Flow-chart of inclusion process of the cohort.



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 (NICU) 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 Figure 1. 63 children born at a gestational age between 24-32 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; (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 6 coronal and 5 sagittal images through the anterior fontanel and mastoid fontanel scanning to detect any cerebellar lesions. Overt brain injury included: IVH grade 2 or higher 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 (PVL) > grade 1 according to de Vries (47) or higher). Criteria 1, 2, 3 and 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, since its crucial impact on language functioning. At age 10 years, 46 of the total of 63 children were willing to participate in the MRI examination in addition to the language, cognition and behavior assessments, during a one-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 (CELF-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 would 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, Wisconsin) using an eight-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 3D 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 mm3. 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 analyse the brain morphology.

Data-processing and brain morphology

Preprocessing of the T1-weighted images was two-fold. 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, artefactual 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 (Fig 1). 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 one-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 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 three speech-language pathologists using Codes for the Human Analysis of Transcripts (CHAT) (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; 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 interrater 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 that 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 gestational age (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 that 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 $p < .025$. 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 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: .11, SD: 1.0) than the non-MRI group (mean : -.52, SD: .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 (β= -.018 (CI= -.073, .038), p=.516), nor with GM volume of right Crus I+II (β=.248 (CI=.011, .485), p=.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=.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 (β=.192 (CI=.033, .351), p=.020) after Bonferroni correction.

For the language structure outcome, the initial multiple linear regression analysis showed no significant relation with total GM cerebellar volume (β=-.005 (CI= -.059, .050), p=.862), nor with GM volume of right Crus I+II (β=.140 (CI= -.093, .372), p=.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 (β=.125 (CI= -.030, .280), p=.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=.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=.044). The association statistically significantly differed between right handed and left handed children, showing a stronger positive association in right handed children.

Table 1. Characteristics, mean language scores and mean cerebellar volumes of study group.

Characteristics Study group (n=42)	**Very preterm (n=63)**
Gestational age (GA) (weeks;days), mean (SD, min-max)	29;2 (1;6, 24;2-31;6)
Birth weight in grams (BW), mean (SD, min-max)	1247 (429, 600-2035)
Female sex, N (%)	17 (41%)
Neighborhood social economic status (NSES), mean (SD)	.08 (.85)
Age at assessment (years;months), mean (SD, min-max)	10;5 (0;7, 9;5-12;0)
ADHD diagnosis, N (%) parent-reported	6 (14%)
Left-handed, N (%)	11 (25%)
Educational level mother, low to high, N (%) 1: High school 2: Secondary vocational education 3: Higher vocational education 4: University level	Unknown: 4 (10%) 1: 6 (14%) 2: 15 (36%) 3: 14 (33%) 4: 3 (7%)
Hearing aid one ear Hearing aids both ears	1 (2% 2 (5%)
Received speech-language therapy in past	21 (50%)
Language scores Renfrew's Bus-story (narrative retelling assessment)	
Language Structure Score, standardized mean score (SD, CI)	-0.44 (.87, -2.3-1.6)
Language Content Score, standardized mean score (SD, CI)	-0.44 (1.00, -2.5-1.9)
Language Structure Score <1 SD, n (%)	12 (29%)
Language Content Score <1 SD, n (%)	15 (36%)
GM Volume Cerebellum/Cerebellar lobules	
Total Cerebellum (cm3), mean (SD)	102.4 (9.1)
Crus I+II right (cm3), mean (SD)	20.6 (2.2)

Table 2. 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.

Dependent variable: Language content			
	B	95% CI	p-value
(Constant)	-5.410	-10.904, .083	.053
Right Crus I+II GM volume (in cm3)	.192	.033, .351	.020*
Gestational Age (in days)	.007	-.021, .036	.592
Sex (males)	-.434	-1.086, .217	.184
Educational Level Parent			.905
1= High school	-.289	-1.660, 1.083	.670
2=Secondary vocational education	-.282	-1.583, 1.019	.661
3=Higher vocational education	-.069	-1.348, 1.209	.913
4=University level	0 (reference)		

Dependent variable: Language structure			
	B	95% CI	p-value
(Constant)	-1.982	-7.334, 3.371	.456
Right Crus I+II GM volume (in cm3)	.125	-.030, .280	.111
Gestational Age (in days)	-.001	-.028, .026	.947
Sex (males)	-.043	-.677, .592	.892
Educational Level Parent			.321
1= High school	-1.195	-2.532, .141	.078
2=Secondary vocational education	-.959	-2.227, .308	.133
3=Higher vocational education	-.751	-1.997, .495	.228
4=University level	0 (reference)		

*statistically significant at the Bonferroni-adjusted significance level of 0.025.

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 (A) and language content scores (B).

Figure 2. Scatter plots of relations between brain measures and language measures. (I.e. total GM cerebellar volume; GM voule of right Crus I+II) and language measures (A. narfrative structure score; B. narrative content score).

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 that were unwilling to do the MRI examination at the age of 10. 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).

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 full term 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 full term 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 full term 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 was 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, since 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.

Acknowledgements

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Appendix A

Additional neuropsychological (i.e. cognitive, behavioral and language) outcomes of study group.

Domain	Outcome measure	Mean (SD, min-max)
Cognition - Wechsler Intelligence Scale for Children-III (WISC-III)	Verbal IQ	96.3 (13.6, 67-126)
	Performance IQ	89.6 (13.9, 65-125)
	Total IQ	92.3 (13.0, 71-124)
Language scores Q-score (mean 100, SD 15)	Vocabulary knowledge - Peabody Picture Vocabulary Task-III (PPVT-III)	99.6 (10.7, 74-120)
	Item-based total language score - Clinical Evaluation of Language Fundamentals, Fourth Edition (CELF-4)	90.1 (14.7, 64-121)
Behavior scores - Child Behavior Checklist (CBCL) T-score: <60=normal; 60-65=subclinical; >65=clinical	Internal problem score	53.5 (5.0, 50-70)
	External problem score	46.3 (10.4, 29-66)
	Attention problem score	56.6 (8.4, 50-77)

Appendix B

Multiple linear regression models with respectively narrative content score and narrative structure score as dependent variable and in (A) total cerebellar GM volume and Right Crus I+II GM volume as the independent outcome variables and in (B) Right Crus I+II GM volume, hand preference (0=right, 1=left) and interaction between handedness and Crus I+II as the independent outcome variables. In all models effects are controlled for gestational age, sex (1=male, 2=female) and educational level of the parent (1=low to 4=high).

A			
Dependent variable: Language content	**B**	**95% CI**	**p-value**
(Constant)	-4.787	-10.668, 1.093	.107
Total cerebellar GM volume	-.018	-.073, .038	.516
Right Crus I+II GM volume (in cm3)	.248	.011, .485	.041
Gestational Age (in days)	.008	-.021, .036	.585
Sex (males)	-.402	-1.068, .264	.227
Educational Level Parent			.870
1= High school	-.311	-1.699, 1.077	.651
2=Secondary vocational education	-.319	-1.639, 1.001	.625
3=Higher vocational education	-.065	-1.357, 1.228	.919
4=University level	0 (reference)		
Dependent variable: Language structure	**B**	**95% CI**	**p-value**
(Constant)	-1.819	-7.586, 3.948	.524
Total cerebellar GM volume	-.005	-.059, .050	.862
Right Crus I+II GM volume (in cm3)	.140	-.093, .372	.230
Gestational Age (in days)	-.001	-.029, .027	.951
Sex (males)	-.034	-.687, .619	.915
Educational Level Parent			.331
1= High school	-1.201	-2.562, .160	.082
2=Secondary vocational education	-.969	-2.264, .325	.137
3=Higher vocational education	-.750	-2.018, .518	.236
4=University level	0 (reference)		

B			
Dependent variable: Language content	**B**	**95% CI**	**p-value**
(Constant)	-2.176	-8.781, 4.428	.506
Right Crus I+II GM volume (in cm3)	.313	.103, .524	.005*
Hand preference (left handed)	-4.830	-10.551, .891	.095
Interaction handedness* Crus I+II	-.242	-.520, .036	.085
Gestational Age (in days)	.004	-.024, .032	.774
Sex (males)	-.535	-1.214, .144	.118
Educational Level Parent			.928
1= High school	-.350	-1.731, 1.031	.608
2=Secondary vocational education	-.379	-1.708, .949	.564
3=Higher vocational education	-.201	-1.495, 1.093	.753
4=University level	0 (reference)		
Dependent variable: Language structure	**B**	**95% CI**	**p-value**
(Constant)	-2.413	-3.681, 8.506	.425
Right Crus I+II GM volume (in cm3)	.286	.092, .480	.005*
Hand preference (left handed)	-6.647	-11.926, -1.369	.015*
Interaction handedness* Crus I+II	-.311	-.568, -.054	.019*
Gestational Age (in days)	-.005	-.031, .021	.687
Sex (males)	-.042	-.669, .584	.891
Educational Level Parent			.148
1= High school	-1.442	-2.716, -.168	.028
2=Secondary vocational education	-1.278	-2.504, -.053	.042
3=Higher vocational education	-1.067	-2.261, .127	.078
4=University level	0 (reference)		

Language functions deserve more attention in follow-up of

Language and brain structures in preterm children: A systematic review

Neurodevelopmental profiles of preterms

Auditory maturation preterm

school-aged children born very preterm

Lateralization in very preterm children

Narrative retelling in preterm born children

Cerebellar volumes and language functions in school-aged

Auditory maturation

Language functions deserve

Language brain

Narrative retelling in preterm

Language functions deserve more attention in follow

Neurodevelopmental profiles of very preterms

Chapter 7

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

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ABSTRACT

Background
Language difficulties of very preterm (VPT) children might be related to weaker cerebral hemispheric lateralization of language. Dichotic listening typically shows a right ear advantage, assuming to reflect left hemispherical language dominance. The corpus callosum (CC), in particular the splenium, is associated with auditory processing and is considered important for language lateralization.

Objective
Exploring whether dichotic listening performance in school-aged VPT children are associated with language performance and interhemispheric connectivity.

Methods
Cross-sectional study 58 VPT children and 30 full term controls at age 10. Language performance and dichotic digit test (DDT) were assessed. In 44 VPT children, additionally, diffusion weighted imaging was performed using a 3T MRI scanner. Fractional anisotropy 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 ($p=.015$). Association between right ear DDT scores and MD of the splenium approached the level of significance ($p=.051$).

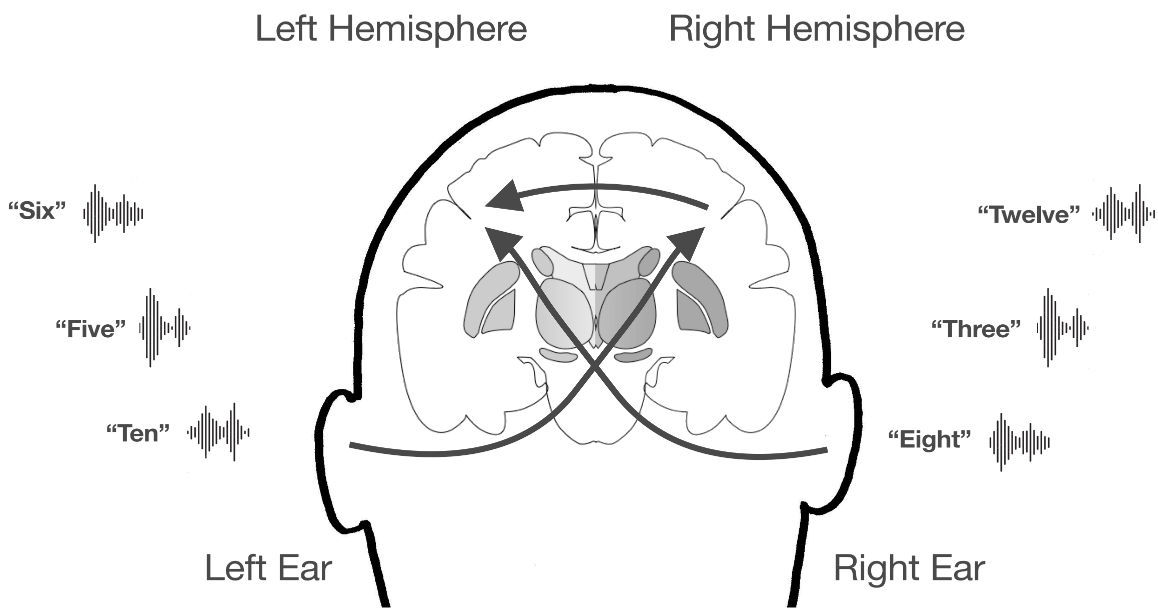
Conclusion
These results support the hypothesis that poor language performance in VPT children may be a consequence of weaker lateralized language organization, due to a poorly developed splenium of the CC. Dichotic listening may reflect the level of language lateralization in VPT children.

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 language tasks until the age of 11-12 (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). Since crossing fibers between auditory nerve and cortex, right ear stimuli are

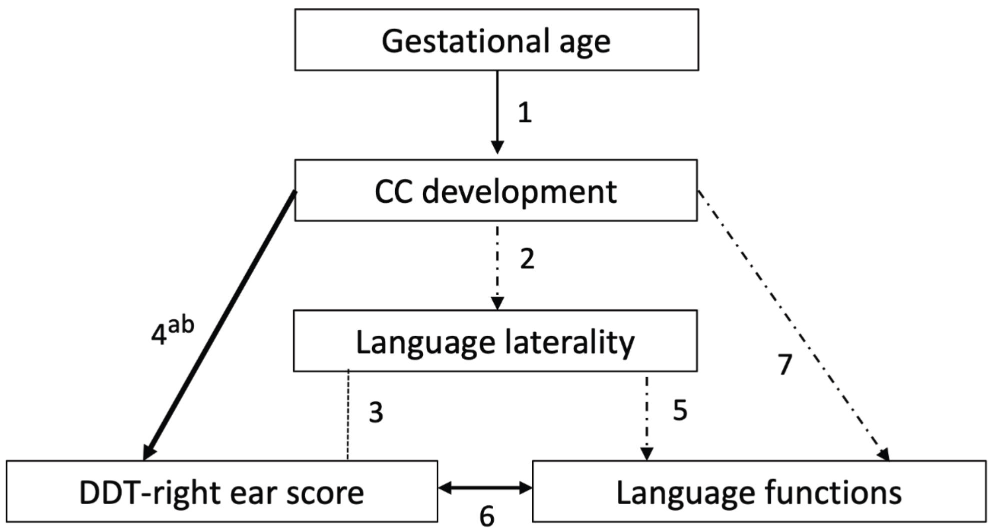
Figure 1. Schematic figure of dichotic listening task (DDT)



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 behavioural 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, Figure 2 schematically shows the theoretical 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

Figure 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 4ab 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.



interhemispheric connections may contribute to explaining the poor language performance of VPT children and may provide evidence for altered language organisation.

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 (RQ's) 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 longitudinal cohort study of language and brain development in children born VPT and had been admitted to the NICU 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 that 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 (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; (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 6 coronal and 5 sagittal images through the anterior fontanel and mastoid fontanel scanning to detect any cerebellar lesions. Overt brain injury included: IVH grade 2 or higher according to Papile (37), post hemorrhagic ventricular dilatation, other brain hemorrhages (including cerebellar hemorrhages), abnormal signal intensity of cortex, or deep GM and WM injury (periventricular leukomalacia (PVL) > grade 1 according to de Vries (38) or higher). Criteria 1, 2, 3 and 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, 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, since its crucial impact on language functioning.

Additionally, structural MRI and diffused weighted imaging (DWI) were performed in 44 of the 63 VPT children, also at the age of 10. 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.

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

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)	VPT group (n=58) vs. FT group (n=30)
Gestational age in weeks;days, mean (SD) median (interquartile range)	29;0 (2;1) 29;4 (27;4-30;6)	29;1 (2.0) 29;3 (27;3-30;5)	39;6 (1.3) 40;0 (39;1-41;0)	p=.490	p<.001
Birth weight in grams, mean (SD) median (interquartile range)	1195 (420) 1118 (855-1626)	1238 (460) 1080 (840-1676)	3469.1 (450) 3450 (3088-3790)	p=.404	p<.001
Female sex, N (%)	25 (43%)	14 (45%)		p=.735	p=.566
Neighborhood social economic status, mean (SD)	-.02 (1.0)	.10 (.92)		p=.338	p=.315
Age (years;months) at assessment, mean (SD)	10;5 (0;8)	10;6 (0;8)		p=.631	p=.132
Left-handed, N (%)	13 (22%)	8 (25%)		p=.507	p=.020
Educational level mother, low to high, N (%)	Unknown: 5 (9%)	Unknown: 3 (10%)		p=.957	p=.051
1: High school	9 (16%)	4 (14%)			
2: Secondary vocational education	20 (34%)	10 (33%)			
3: Higher vocational education	18 (31%)	10 (33%)			
4: University level	6 (10%)	3 (10%)			
DDT and Language scores					
Right ear DDT % correct score (SD), min-max	64.5 (12.2), 22-85	64.8 (10.2), 37-80		p=.839	p=.033
Left ear DDT % correct score (SD), min-max	57.6 (12.8), 25-82	57.1 (13.1), 25-77		p=.767	p=.332
Core language score, Q-score (SD), min-max	89.4 (15.4), 55-129	90.7 (16.1), 55-129		p=.520	p<.001
Diffusion MRI Splenium Corpus Callosum					
FA, mean (SD), min-max		.85 (.04), .77-.93			
MD, mean (SD), min-max		.69 (.06), .59-.78			

Linguistic and Hearing Assessment

Language functions were assessed by a certified speech-language pathologist during a one-day visit to the Erasmus University Medical Centre-Sophia's Children's Hospital. The Core Score of the Clinical Evaluation of Language Fundamentals-4 (CELF-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 (39). The core language score is used to provide an overall language performance index, based on the mean of 4 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.

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 Battery 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 was based on the English version by Kimura (19, 40). The DDT consists of 20 sets of six digits, of which three digits are presented in the right ear and, simultaneously, three 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 (Figure 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. Since 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 for DDT analyses. Hence, 58 of 63 participating VPT born children performed the DDT.

Image Acquisition

MRI was performed on a 3 Tesla scanner Discovery MR750 (General Electric, Milwaukee, Wisconsin) using an eight-channel head coil, located at Erasmus University Medical Centre-Sophia's Children's Hospital in Rotterdam. T1 images were acquired using high-resolution 3D 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 mm3. Additionally, DWI was performed using a 2.5 x 2.5 x 2.5 mm3 resolution and 256 x 256 mm2 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); 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 (41). Pre-processing included Gibb's ringing artefacts removal and eddy currents 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 RQ 1 (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 RQ 2 (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

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. ** p <.005. * p <.05

a. Simple linear regression models (n=88)				**b. Multiple linear regression model (n=88)**				**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	.001	(constant)	39.9	11.9;67.8	.006
DDT right ear	.58	.32;.83	<.001**	Birth group	55.5	19.3; 91.7	.003**	Birth weight	.01	-.003;.02	.193
DDT left ear	.19	-.08;.47	.167	DDT right ear	.18	-.30;.66	.457	DDT right ear	.73	.33;1.13	.001**
DDT right-left difference	.18	-.01;.38	.069	DDT right-left difference	-.10	-.32;.12	.375	DDT right-left difference	-.04	-.33;.24	.766
DDT-right * Birth group	-.16	-.26;-.06	.002*	DDT-right * Birth group	.65	.13;1.17	.015*	Sex (ref=female)	-6.07	-13.3;1.2	.099
FA splenium	-15.2	-152;121	.822	Sex (ref=female)	-4.6	-10.3;1.1	.110	Educational level of the parent			.042*
MD splenium	-51.6	-151;48	.300	Educational level of the parent			.116	Level 1= High school	-12.06	-26.1;2.0	.090
				Level 1= High school	-11.42	-21.6;-1.2	.029	Level 2=Secondary vocational education	1.69	-10.2;13.6	.776
				Level 2=Secondary vocational education	-3.00	-11.7; 5.7	.494	Level 3=Higher vocational education	2.73	-9.2;14.7	.647
				Level 3=Higher vocational education	-1.76	-9.9; 6.3	.666	Level 4=University level	0 (reference)		
				Level 4=University level	0 (reference)						

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 $p < .05$.

Results

Differences between the VPT and FT study groups were not statistically significant for age at assessment (p=.132), sex (p=.566) and neighborhood social economic status (p=.315). The difference in educational level of the mother between VPT and FT children was also not significant, but approached the level of significance (p=.051). Also, there were no statistically significant differences between the VPT subgroup of n=30 and the total VPT group of n=58 (table 1). Mean DDT scores, language scores and mean FA and MD values are presented in table 1 as well.

Regarding RQ 1, a significant association between language outcome and birth group (β=15.7 (CI= 9.2;22.2), p<.001) was found in simple linear regression analyis (table 2a), which means that VPT children have worse language scores than FT children. The association between language outcome and right ear DDT score (β=.58 (CI= .32;.83), p<.001) was also found to be significant (table 2a). The multiple linear regression analysis with the VPT *and* FT children (table 2b), showed a significant interaction effect of birth group and right ear DDT score on language outcome (β= .65 (CI= .13; 1.17), standardized B= 1.1, p=.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 (β=.73 (CI=.33;.1.13), p=.001). In the simple linear regression analyses (table 2a), no significant associations were found between left ear DDT score and language outcome (β=.19 (CI= -.08;.47), p=.167) or the difference between right ear and left ear DDT scores and language outcome (β=.18 (CI= -.01;.38), p=.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 (β=-71.3 (CI= -130.1;-12.6), standardized B= -.4, p=.019). However, when adjusted for sex and birth weight the association did not remain significant, but still approached the level of significance (β=-61.8 (CI=-124.0;.04), p=.051). FA values of the splenium were not significantly associated with the right ear DDT score (β=43.2 (CI=-42.3;128.7), p=.309, table 3). FA and MD values of genu and body were also not associated with the right ear DDT score (Appendix B).

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. In both models adjusted for sex and birth weight.

Multiple linear regression models of VPT subgroup (n=30) Outcome: DDT right ear score				**Multiple linear regression models of VPT subgroup (n=30) Outcome: DDT right ear score**			
	B	95% CI	p-value		B	95% CI	p-value
(constant)	101.5	54.4;148.6	<.001	(constant)	18.9	-55.3;93.2	.605
MD splenium	-61.8	-124.0;.4	.051	FA splenium	43.2	-42.3;128.7	.309
Birth weight	.004	-.004;.012	.290	Birth weight	.007	-.002;.015	.112
Sex (ref=female)	1.1	-6.0;8.2	.750	Sex (ref=female)	2.0	-5.5;9.5	.584

Discussion

The current study revealed that in school-aged children born very preterm, 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 connectivity in the analysis adjusted for sex and birth weight did not reach the level of significance (p=.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 Figure 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 (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 4a) 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, 42). 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 (43). 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 4b) 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, since 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 since only increasing MD was associated with decreasing right ear DDT scores. Increasing MD has been thought to reflect reduced white matter integrity, which might be due to myelin degradation (44). Accordingly, reduced myelin thickness, 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 (45). 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 op 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 distinct 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 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, since 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.

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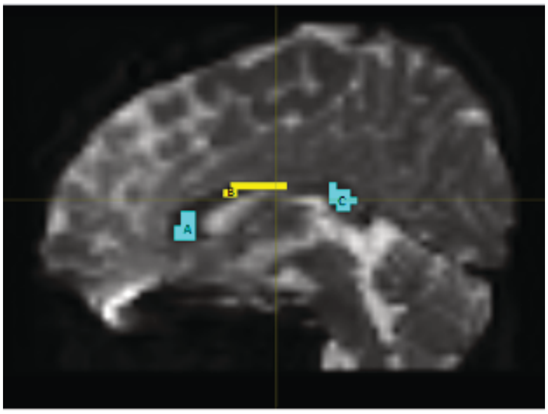
Appendix A

Regions of Interest (ROIs) in Diffusion Weighted Imaging (DWI): (a) genu, (b) body and (c) splenium of the corpus callosum (CC).



Appendix B

Simple and multiple linear regression analyses, with DDT right ear score as the dependent outcome variable and in (A) FA and MD of the genu as the independent variables and in (B) FA and MD of the body as the independent variable

A: Outcome: DDT-right ear score							
Simple models				**Multiple models**			
	B	**95% CI**	**p-value**		**B**	**95% CI**	**p-value**
FA genu	45.5	-42.0;98.1	.419	FA genu	56.5	-33.0;145.9	.206
MD genu	30.8	-49.2;110.9	.437	MD genu	42.9	-38.6;124.4	.290
B: Outcome: DDT-right ear score							
Simple models				**Multiple models**			
	B	**95% CI**	**p-value**		**B**	**95% CI**	**p-value**
FA body	18.4	-49.6;86.3	.584	FA body	21.1	-71.4;113.7	.643
MD body	-8.1	-63.9;47.8	.770	MD body	3.4	-72.4;79.5	.927

Language functions deserve more attention in follow-up of

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

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Chapter 8

Are multidisciplinary neurodevelopmental profiles of very preterm born children at age 2 relevant to their long-term development?

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ABSTRACT

Aim
To identify distinctive multidisciplinary neurodevelopmental profiles of very preterm (VPT) infants and describe the longitudinal course of these profiles up to 10 years of age.

Method
At 2 years of corrected age, 84 VPT infants underwent standardized testing for cognitive, language, speech, motor, behavioural, and auditory nerve function. These data were submitted to factor and cluster analysis. Sixty-one of these children underwent cognitive, language, and behavioural assessment again at 10 years of age. Descriptive statistics were used to analyse longitudinal trajectories for each profile.

Results
Four neurodevelopmental profiles were identified at age 2. Profile 1 infants (n=22/26%) had excellent cognitive-language-motor function, normal behavioural and auditory nerve function, but showed an unexpected severe decline up to 10 years of age. Profile 2 infants (n=16/19%) had very low behavioural function, low cognitive-language-motor function, and accelerated auditory nerve function. Their scores remained low up until age 10. Profile 3 infants (n=17/20%) had delayed auditory nerve function, low behavioural function, and slightly lower cognitive-language-motor function. They showed the most increasing trajectory. Profile 4 infants (n=29/35%) had very low cognitive-language-motor function, normal behavioural and auditory nerve function, but showed wide variation in their trajectory.

Interpretation
Our preliminary study showed that a multidisciplinary profile-oriented approach may be important in VPT children to improve counselling and provide targeted treatment for at risk children. High performers at age 2 may not be expected to maintain their favorable development. Behavioural problems might negatively impact language development. Delayed auditory nerve function might represent a slow start and catch-up development.

Introduction

Children born very preterm (VPT, <32 weeks' gestation) have repeatedly been shown to have neurodevelopmental problems that often persist throughout childhood, and into adolescence (1-9). Several studies have shown developmental problems on single neuro-cognitive domains in VPT children, such as poor cognitive (7), language (5, 10, 11), behavioural problems (12) and delayed auditory conduction time towards and into the brainstem at term equivalent age (13). Moreover, two meta-analyses reported increasing difficulties in VPT children throughout school age, suggesting a growing into deficits effect (5, 9). These results are alarming, since neurodevelopmental problems significantly impact academic abilities and social functioning (14, 15). However, a substantial proportion of VPT children did not have any problems, and a small group even showed a catch-up effect at adolescence (16). So far, the neurodevelopmental trajectory of individual VPT children cannot be predicted. Studying the trajectories of distinctive, multivariate profiles within VPT children, might contribute to early and targeted intervention for those who are truly at risk.

To the best of our knowledge, three studies have used statistical cluster analysis to identify profiles based on outcome measures within one domain in preterm children (17-19). However, so far, no studies have clustered VPT children based on a broad array of neurodevelopmental outcomes at infant age and investigated the long-term trajectories of these outcomes within distinct multidisciplinary profiles. Longitudinal follow-up of neurodevelopmental profiles defined by statistical cluster analysis may provide more comprehensive and clinically meaningful developmental trajectories. Such profiles may clarify which children will catch up, which children will remain stable (either high or low) and which children will grow into deficit. This approach may improve predicting the developmental trajectories of very young VPT children. Early detection of children at risk for long-term neurodevelopmental problems will enable to improve care for VPT children in a timely manner.

Therefore, the first aim of this study was to identify distinctive profiles of VPT infants based on a broad array of neurodevelopmental outcomes (obtained from domain specific tests) by using factor and cluster analysis. The second aim was to describe the longitudinal course of each of the neurodevelopmental profiles defined at infant age. The third aim was to explore whether adding profile membership the context of one of these four profiles to a single outcome, will improve long-term prediction of language, cognitive and behavioural outcomes, compared to prediction without using this membership.

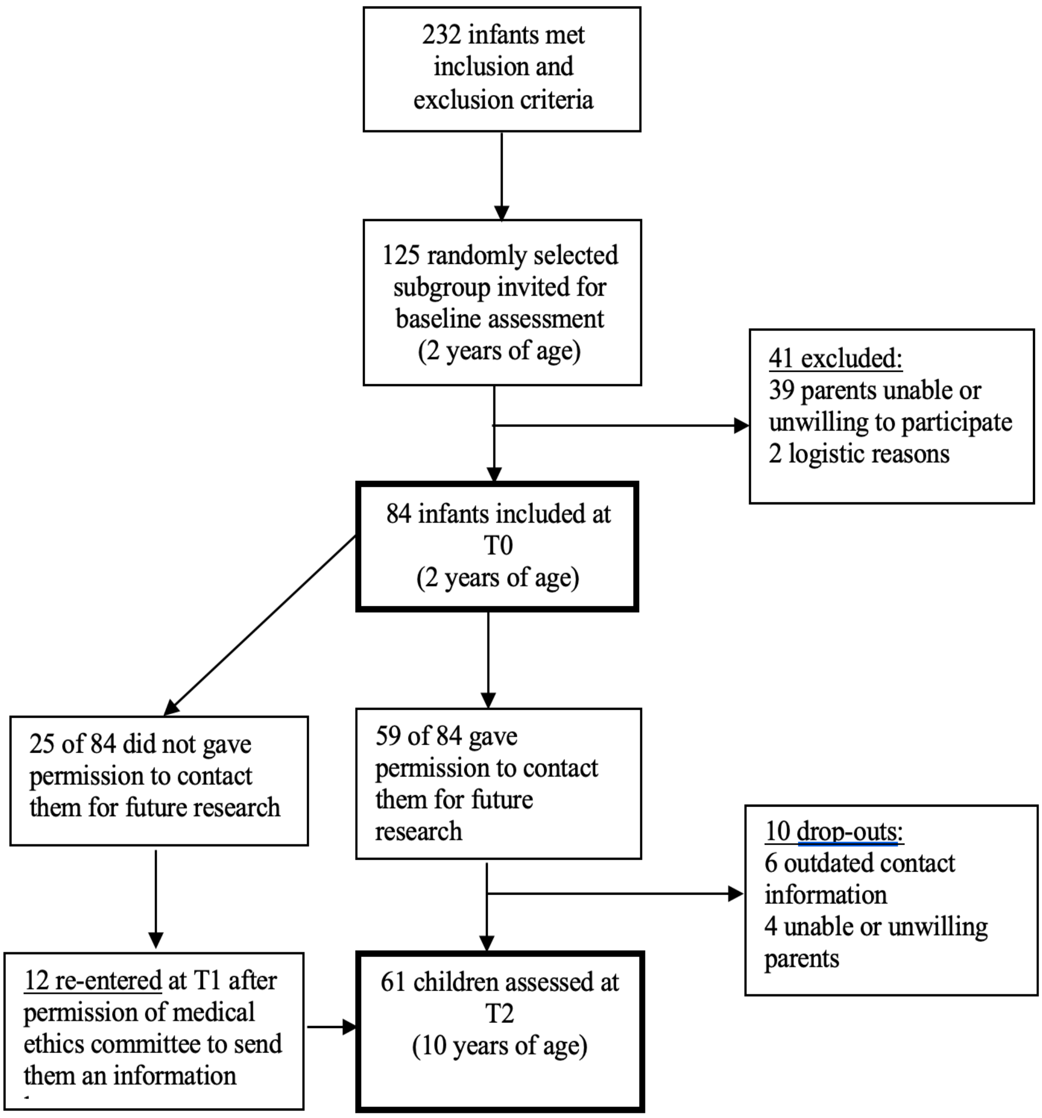
Method

Study group

This study was part of a longitudinal cohort study on speech and language function in VPT children (< 32 weeks' gestation) admitted between October 2005 and September 2008 to a level III neonatal intensive care unit (NICU) at the Erasmus MC-Sophia Children's Hospital Rotterdam. Data used in this study were obtained from assessments at 2 and 10 years. Parents gave written informed consent separately at age 2 and age 10, and the study was approved by the Medical Ethics Committee of Erasmus MC, Rotterdam (MEC-2012-149 and MEC-2015-591).

A total of 232 VPT infants met the inclusion criteria for the cohort study: (1) no severe disabilities (i.e., cerebral palsy with Gross Motor Function Classification System (GMFCS) level >1 or severe vision or hearing disabilities); (2) no congenital abnormalities involving speech organs; (3) no multiple birth; and (4) primary language spoken at home is Dutch. One hundred and twenty-five of them were randomly selected for speech and language

Figure 1. Flow-chart of inclusion process of cohort for each measuring point of longitudinal study.



assessment at 2 years of corrected age (CA), of which 86 could be included because their parents were willing to participate. Because two infants were excluded for logistic reasons, in total 84 infants participated in this study. The study inclusion flow-chart is presented in Figure 1. Of the originally 84 VPT children that were included at the age of 2 years, 59 had given permission to contact them for future research, after the first follow-up at age 4. At the second follow-up, at age 10, 48 children of this group of 59 were assessed again. Besides, with permission of the Medical Ethics Committee, the other 25 children of the original cohort of 84 children had been sent one information letter about the study. The parents of 13 children responded positively and their children were also assessed at age 10 after all. Thus, a total of 61 VPT children gave informed consent for follow-up at 10 years of age.

A comprehensive multidisciplinary assessment as described below was performed at 2 and 10 years of age at the Erasmus MC-Sophia Children's Hospital Rotterdam. Data regarding perinatal and demographic factors were retrieved from the infants' hospital medical records. In addition, data regarding mother's educational level and vocabulary level of one of the parents was collected during the assessments at 10 years of age.

Neurodevelopmental outcomes

Cognitive and Motor function

At age 2 cognitive and motor function were assessed using the Dutch version of the Bayley Scales of Infant Development (BSID, version II or III (20, 21). The BSID-II scores were converted into BSID-III scores, using generally accepted algorithms (22, 23) At age 10, the total intelligence quotient (TIQ) of the Wechsler Intelligence Scale for Children (WISC-III) (24) was used to measure cognitive function.

Language function

At age 2 receptive language function was assessed using the Dutch version of the Reynell Developmental Language Scales (25). Expressive language function was assessed using the Word Development Scale of the Schlichting Test for Language Production (26), and the Dutch Lexilist (27), which is an expressive language checklist completed by the parents.

At age 10 receptive language function was assessed using the Receptive Language Index of the Clinical Evaluation of Language Fundamentals, Fourth Edition (CELF-4) (28). Expressive language function was assessed using the Expressive Language Index of CELF-4. Of 54 of the included children, receptive vocabulary knowledge of either the mother (n=45; 83%) or the father (n=9; 17%) was assessed with the Peabody Picture Vocabulary Task-III (PPVT-III) (29). These scores provide a language-specific familial risk factor. The native language of all parents was Dutch.

Spontaneous speech production

At age 2, speech production was defined by the number of acquired, syllable initial consonants measured by the "Fonologische Analyse van het Nederlands", the Dutch standard assessment of phonological development in children (30). The number of acquired consonants was derived from a speech sample obtained from 20 minutes of child-parent play interaction. By convention, a consonant was considered acquired if it was attempted at least three times and the percentage of correct production was ≥75%. In the absence of norm-referenced data, we considered six or less acquired consonants as abnormal. This criterion was based on our pilot study, in which all 20 term-born controls had acquired at least seven consonants at 2 years of age, range 7-13, median 10.0, mean 9.9 (11). Abnormal speech production was defined as six or less acquired consonants based on a spontaneous speech sample of at least 50 different word realizations or a spontaneous speech sample of less than 50 words combined with a delayed word production (i.e. a score less than 1.5 SD below the mean) based on the parent checklist or the standardized test. Non-classifiable speech production was defined as six or less acquired consonants based on analysis of a speech sample of less than 50 words combined with a normal word production score (i.e. a score more than 1 SD below the mean) on the parent checklist and the standardized test.

Behavioral function

At age 2 behavioural function was assessed using the Dutch version of the Child Behaviour Checklist for ages 1½-5 (31), a validated and norm-referenced parent-report questionnaire. The following four scales were included in the analysis: Internalizing Problems, Externalizing Problems, Attention Problems and Pervasive Problems. Based on the literature, in particular, symptoms of attention disorder and autism spectrum disorder are often observed in VPT infants. Therefore, the attention problems and pervasive problems scales were added. The scales are normalized using a T-scale with a mean of 50 and a standard deviation of 10. For the internalizing and externalizing problem scale, scores between 60 and 63 are considered borderline and scores of 64 or higher are considered clinical. For the attention problem and pervasive problem scale, scores between 65 and 69 are considered borderline and scores of 70 and higher are considered clinical.

At age 10 behavioural function was measured again by parent reporting of the CBCL/6-18 (32). For most cases the CBCL/6-18 was separately completed by the mother and father. In this study only the results of the mother were used (except for two teens of whom only the father had completed the questionnaire). The following four CBCL-scales were included in the analysis: Total Problems, Internalizing Problems, Externalizing Problems, and Attention Problems. In Figure 2 and Figure 3, the behavioural problem scores are presented as z-scores (higher scores refer to less problems), to be easily compared to the cognition and language scores.

Auditory nerve function

Several studies have found a relation between delayed Auditory Brainstem Response (ABR) interpeak latencies and long-term neurodevelopmental problems in preterm children (Majnemer & Rosenblatt, 1996). Preterm birth is assumed to cause atypical brain maturation due to poorer neural myelination, which may result in delayed conduction of auditory stimuli along the auditory nerve into the brainstem. Therefore, at age 2 auditory nerve function was measured by conventional ABR audiometry, using click-evoked stimuli in a soundproof room. No sedation had been given. The waveform obtained at a suprathreshold stimulus level of 70 dB was analysed by at least two experienced clinical specialists defining the post-stimulus peak latencies I (distal cochlear part of the VIIIth nerve), III (in between cochlear nucleus and the superior olivary complex), and V (between the superior olivary complex and the inferior colliculus) in milliseconds. The I-V and III-V interpeak latencies, as a measure of auditory neural myelination, were included as neurodevelopmental outcomes.

At age 10, pure-tone audiometry (0.5, 1, 2 kHz) and tympanometry were performed to measure hearing thresholds, since hearing function can affect oral language functions directly. All hearing measurements were performed in a soundproof booth and according to the ISO standard 8253-1 (33). A computer-based clinical audiometry system (Decos Technology Group, version 210.2.6 with AudioNigma interface) and TDH-39 headphones were used.

All above mentioned assessments were taken by certified professionals and were normed and validated for Dutch children (24, 28, 32). Regarding the standardized tests on cognitive and language function, the raw scores were converted into standard scores based on a mean of 100 and a standard deviation (SD) of 15 (20, 24, 26, 28). By current clinical standards, mild delay was defined as a score between 1 and 2 SD below the mean (score 84-70) and severe delay as a score of >2 SD below the mean (score <70) (24, 28).

Statistical analysis

The statistical analyses were performed using IBM SPSS Statistics version 25 and R version 3.6. Student's T-test, Pearson's chi-square test or Fisher's exact test was used to compare perinatal and demographic factors between the study group and the group of non-participating infants and between each profile. The outcome variables were tested for normality using the Kolmogorov–Smirnov test, with $p<0.05$ indicating that the tested variable distribution differed from a normal distribution. Continuous outcome measures were compared across the clusters using univariate analysis of variance with the Tukey Post hoc test (for normally distributed data) or the Kruskal-Wallis test with the Dunn-Bonferroni post hoc test (for non-normally distributed data). Normally distributed data are presented as mean ± standard deviation. Data that were not normally distributed are presented as median with interquartile range.

Regarding the outcome measure for speech production at age 2, inter-rater reliability was established. An independent experienced clinical linguist re-transcribed the spontaneous language of 13 randomly selected children (15%) and measured the number of acquired consonants for each child. A good reliability was found. The average measure ICC was .872 with a 95% confidence interval from .581 to .961; $F(12,12)=7.817$, $p<0.01$. Tukey's test for nonadditivity showed no interaction; $F(1,12) = 1.027$, $p = 0.33$.

All test scores on cognitive, motor, language and speech function were transformed to z-scores. The scores obtained at age 2 were submitted to factor analysis. The z-scores of the behavioural and the auditory nerve function outcomes were reversed in order to get the same direction of effect for all outcomes; i.e., a higher z-score means a better performance. Kaiser's criterion, eigenvalues >1, was used to define the number of factors to be retained and Varimax rotation was used to determine factor loading.

A cluster analysis with the standardized factor scores was performed based on the data obtained at age 2 to find groups of children that significantly differ from each other on the factors extracted by the factor analysis. First, the optimal number of clusters was determined by means of a hierarchical cluster analysis according to Ward (34). Second, a K-means cluster analysis over the same factor scores was applied based on the number of clusters indicated by Ward's dendrogram. The cluster centers obtained with the hierarchical cluster analysis were used as the initial values for the K-means cluster analysis.

The Kruskal-Wallis test with the Dunn-Bonferroni post hoc test and chi-square tests were used to determine whether perinatal and demographic factors were associated with clusters.

To ascertain whether the definition of the neurodevelopmental profiles at infant age improved the prediction of cognitive, language and behavioural outcome measures at school age, compared to the prediction based on single domain outcome measures, linear regression models were used. More specifically, for each single domain outcome measure (i.e. receptive language; expressive language; cognitive function; internalizing behaviour; externalizing behaviour; attention problems) a separate linear regression model was used. An outcome measure at age 2 and profile membership were entered as independent variables and the corresponding outcome measure at age 10 was entered as the dependent variable. Furthermore, different profile trajectories were compared as descriptive statistics as well. To investigate the sensitivity to outliers in a sensitivity analysis, we applied robust regression models using the Huber method, effectively down-weighing outliers in the analyses. All statistical tests were two sided and statistical significance was defined at $p < .05$. Adjustment for multiple testing was performed by using a bonferroni correction. Since 16 p-values were relevant in the regression models, statistical significance was reached when $p < 0.05/16$ or 0.003.

Missing data at age 2 were replaced for the purpose of the factor-analysis by means of Expectation Maximization (Little's MCAR test: Chi-square=74.536, DF=71, p=.364). Missing data resulted from either examiner error or child noncompliance. The proportion of missing values was 6.0% (n=5) for cognitive function; 4.8% (n=4) for word production; 3.6% (n=3) for behavioural function; 17.9% (n=15) for motor function; and 13.1% (n=11) for auditory nerve function.

Results

The 84 infants assessed at age 2 had a mean birth weight of 1173 ± 392 grams and mean gestational age of 29 ± 2 weeks. The characteristics of the study group did not significantly differ from the non-participating group, n=41 (Appendix A). The characteristics of the participating group at age 10, n=61, did neither significantly differ from the non-participating group, n=23 (Appendix A).The neurodevelopmental outcomes of the infants at age 2 are presented in Appendix B. The mean scores on these outcomes were within the normal range, except for speech production, which was abnormal in almost half of the infants.

Factor and cluster analysis at age 2

A scree plot and eigenvalue analyses indicated that three factors could be extracted which explained 69% of the total variance in the neurodevelopmental outcomes of the VPT infants. The eigenvalues for the three factors were respectively 3.9, 2.7 and 1.7. Therefore, the number of factors was set to three for the subsequent varimax rotation analysis. The factor matrices were then examined and factors defined in terms of variables with a loading of .5 or larger. The results of the factor analysis with Varimax rotation are presented in Table 1.

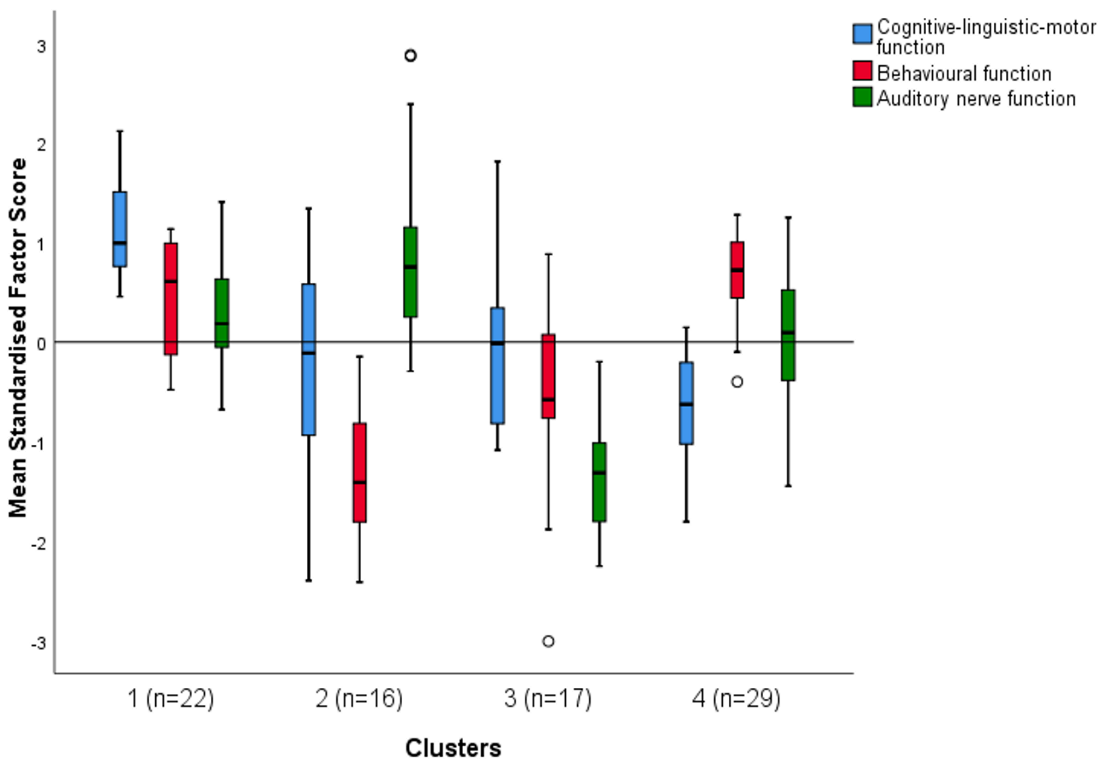
The first factor included cognitive, motor, language, and speech outcomes and we labelled this 'cognitive-motor-language function'. The second factor we labelled 'behavioural function' because it was clearly defined by aspects of behavioural function. The third factor we labelled 'auditory nerve function' because the I-V and III-V interval latencies were found to load high on this factor.

A dendrogram of the Ward's hierarchical cluster analysis based on the three factors of the factor analysis showed that the neurodevelopmental outcomes clustered into four groups. A K-means cluster analysis was then conducted with a restriction to four clusters. Figure 2 displays boxplots of these four clusters. The units on the vertical axis are standard deviations from the mean of the standardized factor scores (M=0 and SD=1). A high mean

Table 1. Factor-analysis with Varimax rotation on neurodevelopmental outcomes in very preterm infants at 2 years of corrected age (n=84).

Outcomes	Factor 1	Factor 2	Factor 3
Cognitive composite score	.81	.13	-.04
Receptive language quotient	.78	.11	-.13
Word production quotient	.85	.07	.01
Lexilist quotient	.83	.09	-.07
Spontaneous speech production score	.84	-.07	-.04
Motor composite score	.60	-.05	-.50
Internalizing problems score	.06	.82	-.31
Externalizing problems score	.10	.89	-.03
Attention problems score	-.13	.76	-.05
Pervasive problems score	.28	.78	.19
I-V interval latency in ms	-.06	-.01	.85
III-V interval latency in ms	-.08	-.12	.76

Figure 2. Boxplot illustrating the results of K-means cluster analysis for the very preterm infants based on their neuro-developmental outcomes.



factor score indicates that the cluster of infants had a relatively good performance on this specific factor.

Profile 1 (n=22; 26%) consisted of infants with the highest scores in all neurodevelopmental domains. We named this group: neurodevelopmental high performers. Profile 2 (n=16; 19%) consisted of infants with the lowest behavioural function, lower cognitive-language-motor function, and high auditory nerve function. We named this group: very low behavioural function and markedly accelerated auditory nerve function. Profile 3 (n=17; 20%) consisted of infants with delayed auditory nerve function, low behavioural function, and slightly lower cognitive-language-motor function. We named this group: mild neurodevelopmental delay with delayed auditory nerve function. Profile 4 (n=29; 35%) consisted of infants with the lowest cognitive-language-motor function, normal behavioural and auditory nerve function. We named this group: poor neurodevelopmental functioning but no behavioural problems. Table 2 presents a detailed picture of the neurodevelopmental outcome scores for each profile. The first profile had high-average mean scores on all domains. The second profile had average mean scores for cognition, motor, and language function. However, they stand out in abnormal behavioural function, below-average speech production as well as the shortest mean ABR interval latencies, indicating accelerated auditory nerve function. The third profile had mean scores in the high-average to low-average range for cognitive, motor, language and behavioural

Table 2. Neurodevelopmental outcomes for each of the four profiles of very preterm infants at 2 years of corrected age (n=84).

Outcomes	Profile 1 (n=22)	Profile 2 (n=16)	Profile 3 (n=17)	Profile 4 (n=29)
Cognitive composite score, mean (SD)	113.7 (6.1)	100.5 (12.3)	103.4 (8.7)	98.9 (8.9)
Receptive language quotient, mean (SD)	109.1 (10.3)	86.1 (18.2)	89.8 (13.2)	84.1 (17.0)
Word production quotient, mean (SD)	107.4 (9.6)	90.3 (9.7)	92.8 (10.6)	85.6 (8.6)
Lexilist quotient, mean (SD)	103.9 (10.6)	83.1 (13.3)	90.4 (12.3)	79.9 (12.1)
Spontaneous speech production score, mean (SD)	9.9 (2.5)	6.2 (3.6)	6.2 (2.8)	4.3 (2.6)
Motor Composite score, median (IQR)	107 (104-113)	98 (86-103)	110 (96-126)	98 (94-104)
Internalizing problems score,[a] median (IQR)	51 (50-53)	63 (58-66)	53 (51-56)	50 (50-51)
Externalizing problems score,[a] median (IQR)	37 (36-45)	60 (56-62)	51 (45-58)	41 (37-45)
Attention problems score,[a] median (IQR)	52 (50-62)	62 (54-70)	56 (52-60)	51 (50-52)
Pervasive problems score,[a] median (IQR)	50 (50-51)	59 (52-68)	56 (52-63)	51 (50-52)
I-V interval latency in ms, median (IQR)	4.2 (4.1-4.2)	4.1 (3.9-4.2)	4.4 (4.3-4.4)	4.2 (4.0-4.3)
III-V interval latency in ms, median (IQR)	1.9 (1.8-2.0)	1.8 (1.7-2.0)	2.1 (2.1-2.2)	1.9 (1.9-2.0)

The behavioural problems scale is inverse, so a higher score indicates lower performance.

function. This profile, however, had the longest mean ABR interval latencies, indicating delayed auditory nerve function, and below-average speech production. The fourth profile had low to below-average mean scores specifically for language and speech function.

Perinatal and demographic characteristics for each profile at 2 years of corrected age are shown in Table 3. Only total days of invasive mechanical ventilation was statistically significantly different among the profiles at 2 years of corrected age (Kruskal-Wallis X2 [4] = 9.679; p= .021) since cluster 2 showed a higher number of total days of invasive mechanical ventilation than cluster 1 (p= .019).

Profile trajectories

From the VPT children who participated at 2 and 10 years of age (n=61), there were 16 children with profile 1 (73% of original 22), 11 children with profile 2 (69% of original 16), 10 children with profile 3 (59% of original 17) and 24 with profile 4 (83% of original 29). Table 3 also presents the perinatal and demographic characteristics of the VPT children included at follow-up at age 10. No significant differences were found between the four profiles on birth weight (BW), male sex, neighbourhood socioeconomic status (SES), total days of stay in the NICU, and total days of invasive mechanical ventilation. However, GA (F(3.57)= 3.382, p= .024) and parent's receptive vocabulary score did significantly differ among the profiles (F(3,49)= 3.982, p= .013). A Tukey post hoc test revealed that in the study group of the current study (N=61) mean GA was significantly lower in profile 2 children (27.7±2.0) compared to profile 3 children (30.0±1.3, p= .042), while there were no significant differences between GA of the four profiles at the original cohort at infant age (n=84). Mean parent's receptive vocabulary score was significantly lower in profile 2 children (84±12.0) compared to profile 1 children (98±8.0, p= .020) as well as compared to profile 4 children (97±11.4, p= .018). Furthermore, mother's educational level was also significantly different among profiles (x2(9, N=56)=21.49, p=.011). However, after Bonferroni-correction because of the 16 comparisons, no significant difference among the profiles was found.

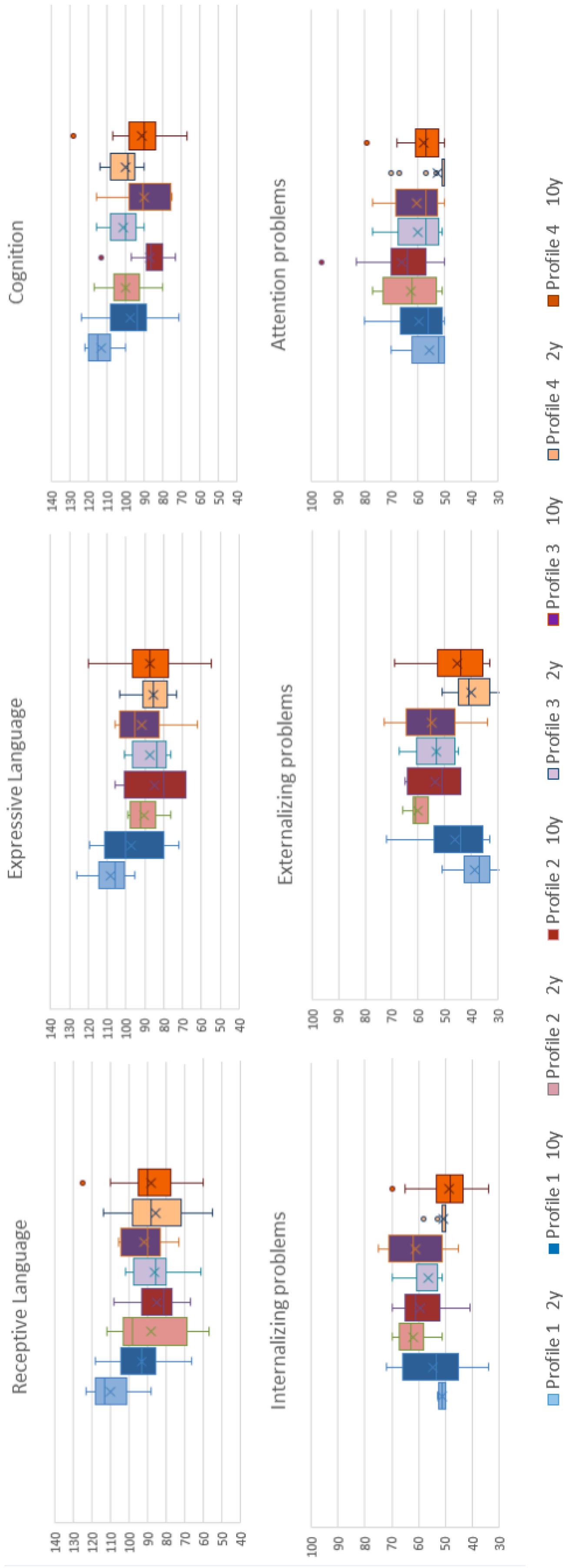
Regarding the second research question, descriptive statistics indicated different neurodevelopmental trajectories for each profile (Table 4, Figure 3 and 4). Children with profile 1 showed a sharp decrease in the language and cognitive outcomes, which was not expected from their favourable scores at the age of 2. They maintained neurodevelopmental scores within normal limits at 10 years of age, but overall, at 10 years of age, their scores were approximately 1 SD lower than the mean score at age 2. Children with profile 2, who were characterized by behavioural problems and accelerated auditory nerve function at age 2, showed the expected worse development, showing the lowest scores at the age of 10 for all outcome measures, of all four profiles. In contrast, children with profile 3, who were characterized by mild neurodevelopmental delay with behavioural problems, unexpectedly showed the most increasing trajectory of all four profiles. At age

Table 3. Perinatal and demographic characteristics for each of the four neurodevelopmental profiles of very preterm children at 2 and 10 years of age.

	Profile 1		Profile 2		Profile 3		Profile 4	
	Age 2 N=22	**Age 10 N=16**	**Age 2 N=16**	**Age 10 N=11**	**Age 2 N=17**	**Age 10 N=10**	**Age 2 N=29**	**Age 10 N=24**
Gestational age, wk, mean (SD)	29.6 (1.5)	29.7 (1.5)	28.0 (1.9)	27.7 (2.0)	29.8 (1.4)	30.0 (1.2)	28.6 (2.4)	28.6 (2.4)
Birth weight, grams, mean (SD)	1234.1 (431.1)	1281.6(425.5)	1020.6 (349.6)	1001.8(313.3)	1282.9(335.8)	1312.0(391.8)	1147.1 (402.0)	1148.3(421.0
Male sex, n (%)	11 (50)	8 (50)	12 (75)	7 (64)	10 (59)	6 (60)	18 (62)	15 (62)
Neonatal brain injury[a], n (%)	1 (5)	1 (6)	2 (13)	2 (18)	1 (6)	1 (10)	2 (7)	2 (8)
Perinatal inflammation[b], n (%)	9 (41)	6 (38)	7 (44)	4 (36)	10 (59)	6 (60)	17 (59)	12 (50)
Total days of invasive mechanical ventilation, mean (SD)	2.0 (3.4)	2.2 (3.9)	11.3 (13.2)	10.5 (9.6)	3.5 (5.7)	2.6 (3.7)	8.2 (12.7)	8.4 (13.5)
Total days of stay in neonatal care unit, mean (SD)	19.2 (15.0)	17.5 (16.0)	27.3 (20.4)	26.6 (15.5)	16.4 (14.3)	15.0 (11.9)	28.9 (30.2)	30.1 (31.8)
Neighborhood socioeconomic status[c], mean (SD)	-0.17 (0.86)	-0.31 (0.88)	-0.17 (1.35)	0.46 (1.60)	.01 (0.65)	-0.04 (1.23)	-0.03 (0.93)	0.01 (1.09)
Educational level mother (parent-reported at age 10), low to high, n (%)*								
1: High school	-	3 (19)	-	2 (18)	-	1 (10)	-	5 (21)
2: Intermediate vocational education	-	4 (25)	-	7 (64)	-	1 (10)	-	9 (37)
3: Higher vocational education	-	8 (50)	-	0	-	7 (70)	-	4 (17)
4: University level	-	0	-	0	-	1 (10)	-	4 (17)
Unknown	-	1 (6)	-	2 (18)	-	0	-	2 (8)
Receptive vocabulary parent, mean (SD)*	-	98 (7.9)	-	84.1 (12.0)	-	91.8 (10.8)	-	96.7 (11.4)
Hearing threshold of one ear above 20 dB – wearing hearing aid, n (%)	-	1 (6)	-	0	-	0	-	3 (13)- 1 (4)
Hearing threshold of both ears above 20 dB – wearing hearing aids, n (%)	-	0	-	1 (9) – 1 (9)	-	0	-	1 (4)
ADHD diagnosis (parent-reported at age 10), n (%)	-	1 (6)	-	4 (36)	-	2 (20)	-	3 (13)
Left-handed (parent-reported at age 10), n (%)	-	3 (19)	-	2 (18)	-	2 (20)	-	7 (29)
Special school services (parent-reported at age 10), n (%)	-	0	-	2 (18)	-	1 (10)	-	4 (17)
Received speech-language therapy (parent-reported at age 10), n (%)	-	4 (25)	-	7 (64)	-	4 (40)	-	17 (71)

[a]neonatal brain injury (i.e. intraventricular haemorrhage grade II-IV and infarction). None of the children included in this study had cystic periventricular leukomalacia (c-PVL). Since the detection of less severe grades of PVL is difficult we did not include this prenatal factor in the group of 'neonatal brain injury'; [b]perinatal inflammation (i.e. neonatal proven sepsis, premature rupture of the membranes or chorioamnionitis); [c]neighbourhood socioeconomic status (SES; Knol et al., 2012). This score ranges from +3.4 to –5.2 and is based on income, occupation, and education. Scores >0 are considered high SES and scores ≤0 low SES. *There were missing values for two variables: "Educational level mother" (displayed in table) and "Receptive vocabulary parent" (i.e. missing values Profile 1 N=4, Profile 2 N=1, Profile 3 N=0, Profile 4 N=3). P-values were calculated with univariate analysis of variance or Pearson's chi-square test. All comparisons were $p>0.05$

Figure 3. Box plots of the neurodevelopmental outcomes at 2 and 10 years of age for each of the four profiles.

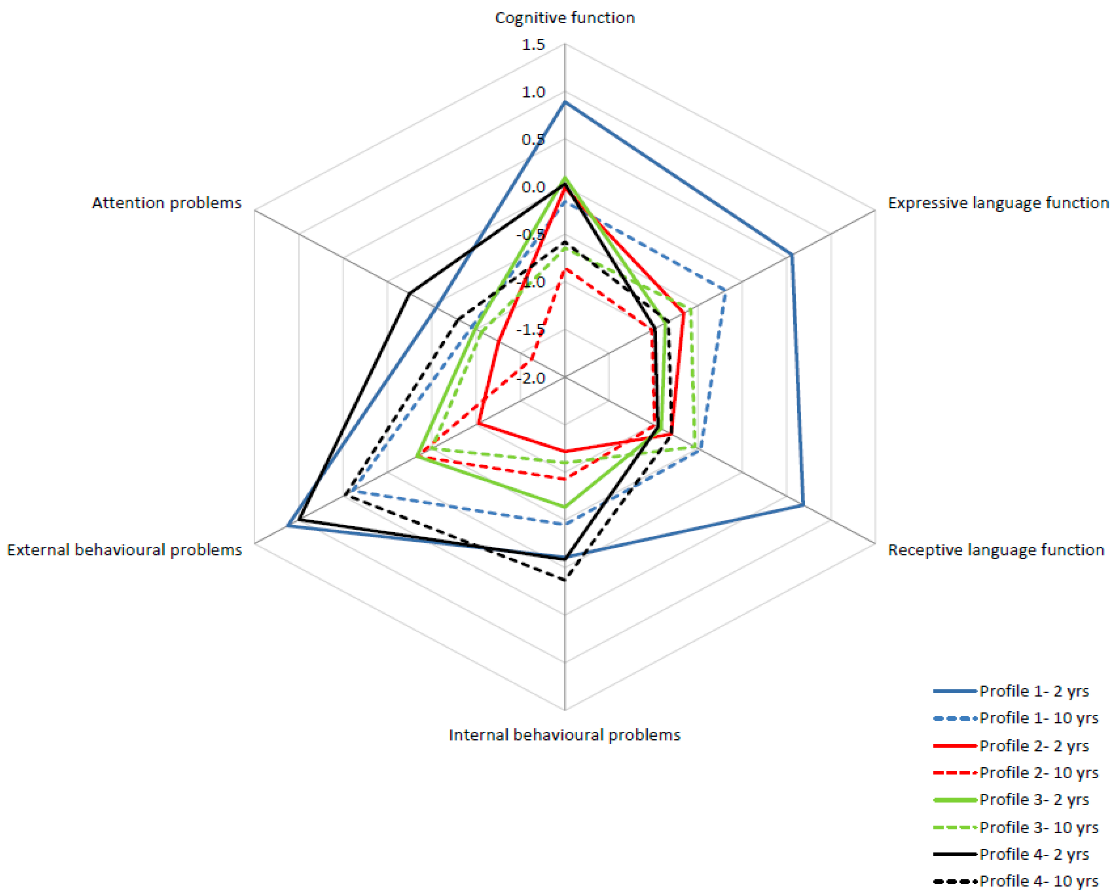


10, children with profile 3 had a better outcome compared to children with profiles 2 and 4 and even approached the outcomes of profile 1, at 10 years of age. However, their mean total behavioural problems increased. The trajectories of the children with profile 4 showed the largest variation, compared to the other profiles, but mean language scores remained almost 1 SD below the mean. They showed severely increased mean attention problem score and mean total behaviour problem score (41% and 21% respectively).

Mean cognition scores decreased in all profiles, however, the largest difference (16 Q-points, 14%) occurred in children with profile 1, the neurodevelopmental high performers, compared to 13%, 11% and 9% in profile 2, 3 and 4 respectively.

Regarding the third research question, all neurodevelopmental outcome scores at age 10 were regressed on those at age 2 and profile membership. Profile membership was not statistically significant for any of the outcomes. This result did not change when robust regression was used.

Figure 4. Radar chart of the neurodevelopmental outcomes at 2 and 10 years of age for each of the four profiles.



Data are presented in standardised mean-scores for all variables; high scores refer to favorable results for all outcome measures.

Discussion

This preliminary study showed that a multidisciplinary profile-oriented approach may be important in VPT children to improve counselling and provide targeted treatment for at risk children. A factor and cluster analysis based on a broad array of neurodevelopmental outcomes obtained at 2 years CA revealed four distinctive profiles of VPT infants. The longitudinal course of these multidisciplinary profiles from 2 to 10 years of age, as well as the profile differences on single domain outcome trajectories is presented. Despite very preterm birth, about one quarter of the infants performed well on all investigated neurodevelopmental outcomes, cognitive-language-motor, behavioural, and auditory nerve function – the profile 1 infants. However, these children showed an unexpected serious decline up to 10 years of age. Since they had the most favourable cognitive-language-motor function scores at age 2, the results at age 10 could be reflecting a regression to the mean. Another explanation, however, might be the relatively high vocabulary scores of the parents of children with this profile. At infant age these children may have benefited from living in an environment with relatively rich language input. At school age, neurodevelopmental functioning becomes more complex, entailing integration across different neurocognitive domains. This increasing complexity might have led to diminishing developmental scores over time, resulting in a 'growing into deficits effect'. This effect has been defined as cumulative, increasing neurodevelopmental problems throughout childhood due to early brain damage (35). If this trend could be validated in larger samples, such a declining development would be critical to clinical practice. Then, it would be highly relevant to study whether extra cognitive-linguistic stimulation (by parents or a treatment program) will sustain their favourable early development. Another explanation might be that these children cannot keep up with their head start, due to altered brain development. VPT children have been suggested to have delayed language lateralization (36), which might explain the 'growing into deficits effect' for children with favourable scores at age 2.

All other infants had below-average mean scores in at least one neurodevelopmental domain at the age of 2 – profile 2, 3 and 4 infants. However, based on visual inspection of the data in graphs (Figure 4), these children showed different trajectories dependent on their profile membership. Profile 2 infants were mainly characterized by behavioural problems at age 2. Interestingly, this aspect goes together with shorter ABR latencies, which has no known clinical implications but may be a marker of abnormal neural function (13). A possible reason for shortened ABR latencies may be a shorter neural trajectory due to smaller head size (37). However, in the present study, the shorter latencies could not be explained by a significantly shorter head circumference at two years of age in profile 2 infants compared to the infants in the three other profiles. The trajectory of profile 2 children showed a decline, while children with mild neurodevelopmental delay with behavioural problems (profile 3) showed a catch-up, and children with poor neurodevelopmental functioning (without behavioural problems or delayed auditory nerve

Table 4. Language, cognitive, and behavioural outcomes at age 2 and 10 for each of the four profiles of the very preterm children

	Profile 1 N=16		Profile 2 (N=11)		Profile 3 (N=10)		Profile 4 (N=24)		Total (N=61)	
	Mean (SD) 2 years	10 years	Mean (SD) 2 years	10 years	Mean (SD) 2 years	10 years	Mean (SD) 2 years	10 years	Mean (SD) 2 years	10 years
Language										
Receptive language quotient, mean (SD)	110.3 (10.5)	92.9 (15.1)	88.0 (19.2)	85.2 (13.1)	86.3 (12.5)	92.0 (12.4)	85.7 (17.4)	88.1 (13.9)	92.7 (18.5)	89.5 (13.8)
Word production quotient, mean (SD)	108.4 (9.4)	-	90.1 (7.9)	-	87.0 (9.1)	-	85.3 (8.6)	-	92.5 (13.0)	-
Expressive language quotient, mean (SD)	-	97.2 (16.0)	-	84.7 (14.8)	-	91.3 (14.0)	-	87.5 (14.9)	-	90.2 (15.4)
Cognition										
Cognitive composite score, mean (SD)	113.3 (6.6)	-	99.8 (11.1)		101.4 (8.3)		100.4 (7.6)		103.9 (9.8)	
Verbal IQ, mean (SD)	-	101.0 (14.2)	-	89.6 (13.9)	-	96.2 (11.7)	-	94.6 (12.3)	-	95.7 (13.3)
Performance IQ, mean (SD)	-	94.3 (15.1)	-	87.7 (11.7)	-	86.1 (14.6)	-	89.7 (15.3)	-	90.0 (14.5)
Total IQ, mean (SD)	-	97.6 (14.1)	-	87.2 (10.7)	-	90.3 (13.8)	-	91.3 (12.8)	-	92.1 (13.2)
Behaviour										
Total problems score, mean (SD)	46.4 (10.6)	52.7 (12.1)	60.7 (8.1)	62.3 (12.6)	53.7 (5.1)	60.5 (10.0)	41.2 (9.5)	49.7 (9.3)	48.1 (11.5)	54.5 (11.8)
Internalizing problems score, mean (SD)	51.1 (1.2)	54.5 (11.9)	62.2 (5.7)	59.3 (8.9)	56.3 (6.3)	61.0 (10.4)	50.8 (1.7)	48.7 (9.7)	53.9 (5.7)	54.1 (11.2)
Externalizing problems score, mean (SD)	38.8 (6.5)	46.1 (11.4)	60.3 (3.3)	53.4 (8.3)	53.3 (7.9)	55.0 (12.6)	40.0 (6.3)	45.3 (10.5)	45.5 (10.6)	48.5 (11.3)
Attention problems score, mean (SD)	55.5 (7.3)	59.5 (9.7)	62.6 (9.1)	66.3 (13.2)	59.9 (9.6)	60.6 (9.1)	41.2 (9.5)	58.0 (7.2)	56.3 (8.1)	60.3 (9.7)
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Receptive language quotient <-1SD, n (%)	0	3 (25)	5 (45)	6 (55)		5 (50)	2 (20)	10 (42)	9 (38)	20 (33)
Expressive language quotient <-1SD, n (%)	0	4 (25)	4 (36)	6 (55)	6 (60)	3 (30)	12 (50)	9 (38)	22 (36)	22 (36%)
VIQ <-1 SD, n (%)	-	2 (13)	-	2 (18)	-	2 (20)	-	4 (17)	-	10 (16%)
PIQ <-1 SD, n (%)	-	4 (25)	-	4 (36)	-	5 (50)	-	10 (42)	-	23 (38%)
Cognitive composite score <-1 SD, n (%)	0	-	1 (9)	-	0	-	0	-	1 (2)	-
Disharmonic IQ profile, n (%)	-	7 (44)	-	4 (36)	-	3 (30)	-	10 (43)		
Total behaviour problems score										
Clinical range, n (%)	0	4 (25)	4 (36)	4 (36)	0	4 (40)	0	2 (8)	4 (7)	14 (23%)
Borderline range, n (%)	2 (13)	2 (13)	1 (9)	0	1 (10)	2 (20)	0	1 (4)	4 (7)	5 (8%)
Internalizing problems score										
Clinical range, n (%)	0	5 (31)	3 (27)	4 (36)	1 (10)	4 (40)	0	2 (8)	4 (7)	15 (25%)
Borderline range, n (%)	0	1 (6)	4 (36)	3 (27)	1 (10)	2 (20)	0	1 (4)	5 (8)	7 (11%)
Externalizing problems score										
Clinical range, n (%)	0	1 (6)	1 (9)	3 (27)	1 (10)	2 (20)	0	3 (13)	2 (3)	9 (15%)
Borderline range, n (%)	0	1 (6)	5 (45)	0	1 (10)	1 (10)	0	0	6 (10)	2 (3%)
Attention problems score										
Clinical range, n (%)	1 (6)	2 (13)	3 (27)	3 (27)	2 (20)	2 (20)	1 (4)	1 (4)	7 (11)	8 (13%)
Borderline range, n (%)	2 (13)	3 (25)	1 (9)	2 (18)	0	2 (20)	1 (4)	3 (13)	4 (7)	10 (16%)

function, profile 4) showed the widest variation in their trajectory.

A possible explanation for the favorable development of profile 3 children might be that these children represent 'slow starters'. Their delayed auditory nerve function at age 2 might reflect delayed, but not disordered, brain maturation, followed by a catch-up development in the following years. Thus, delayed auditory nerve function might be associated with low performance at age 2, but might reflect increased performance at school-age.

Another explanation for the different trajectories of profile 2 and profile 3 children might be found in behavioural problems at infant age, since behaviour scores differed significantly between children with profile 2 and 3 at infant age. More behavioural problems, as children with profile 2 were found to have, might have negatively impacted their language development, since their language scores declined the most. Accordingly, less behavioural problems, as profile 3 children were found to have, might have been favorable for their language development. This is in line with previous research suggesting that early behavioural problems have a negative impact on long-term cognitive and language outcome in VPT children (12). The difference in language development between profile 2 and 3 children might also be explained by perinatal factors. Mean GA was significantly lower in profile 2 children than in profile 3 children.

Children with profile 4 showed the widest variation on all outcome measures at the age of 10 years. This might be explained by the fact that neonatal factors such as GA and neonatal illness varied the most in profile 4 children. Children with lower GA or more severe neonatal illness are expected to have a stable low trajectory, while children with a more favourable neonatal base are expected to have increasing development (38, 39).

Regarding cognitive function, our preliminary data showed diminishing scores between 2 and 10 years of age in all four profiles, suggesting a growing into deficits effect. This has not been expected, since longitudinal studies have shown stable cognitive development throughout childhood (40, 41). However, Wong et al. showed that early developmental assessments such as the BSID have poor sensitivity for long-term cognitive development, which is in accordance with our results showing a majority of children with lower cognitive scores at school age (assessed with WISC-III) than at infant age (assessed with BSID). The results of the current study also provided evidence for the idea that the BSID may not be sensitive enough to detect cognitive deficits at infant age. Since the BSID is regularly used in clinical practice, these findings are alarming and show the importance of longitudinal follow-up of all VPT children.

Previous research has repeatedly shown boys to have lower neurocognitive scores, including language scores, than girls (39, 42, 43). Therefore, as an additional analysis, the longitudinal language trajectories of boys and girls was explored separately. In the cohort of the current study, boys also performed worse than girls at the age of 2, specifically on receptive language outcome (mean receptive language score boys: 86.1 (SD 19.1), girls: 102.2 (SD 12.7), independent samples t-test p=.001). However, boys, more often than girls, have a neurodevelopmental profile with a catch-up trajectory, which is in accordance with results of Doyle et al. (44). Moreover, girls had diminishing receptive language outcomes at the age of 10 (mean receptive language score girls: 92.2 (SD 13.9), paired samples t-test p=.007), resulting in equal receptive language outcomes for boys and girls at age 10 (mean receptive language score boys age 10: 87.6 (SD 13.7). Therefore, boys may have a "slow to warm up" development, while girls show a "head start", but do not maintain this more advanced development when they reach school age

Strengths and limitations

This study is the first to use factor- and cluster-analysis based on a broad array of included neurodevelopmental outcomes obtained from domain specific tests. The method of longitudinally analyzing these multiple neurodevelopmental outcomes within the framework of four distinctive neurodevelopmental profiles is unique. This 'profile-view' is a person-oriented approach, where the child and his coherent neurodevelopment are centralized, instead of one specific scientific field. The main limitation of this study is its small sample size. Since we followed-up four profiles, the power of each individual profile remained insufficient for adequate statistical analysis. Unfortunately, due to the small sample size, it was not possible to study sex differences within each profile, for example. Furthermore, we studied a wide timeline, from 2 to 10 years of age, which covers a period in which a child is exposed to many different influencing factors, at home and school, in an academic and social way, leading to an enormous amount of environmental variety. Also, a control group could have provided more insight in the specificity of the developmental patterns, although our main aim was to better understand the developmental differences within VPT children.

Further research and implications

We strongly recommend other researchers to study larger samples of VPT children and use profile analysis based on at least language, cognitive and behavioural outcome to describe the longitudinal, multidisciplinary development of VPT children adequately. Future studies with larger sample sizes are also needed to explore the idea of a mediate on language development as well as the impact of neonatal factors, such as GA, on clustered neurodevelopmental trajectories. In addition, with a larger sample it might be possible to explain the wide variability as found in profile 4 children (i.e. poor neurodevelopmental functioning but normal behavioural and auditory nerve function) in this study, by studying the impact of GA and neonatal illness on their development. It may also be relevant to include sex as an interacting factor that may add to a better prediction of the neurodevelopmental trajectories. If our results could be confirmed in larger samples, this wide variability would suggest that these children have to be monitored intensively. Furthermore, it would also be recommendable to compare the development of VPT children's profiles to those of term-born peers to find out whether the different developmental patterns are typically for VPT children only. If our preliminary results could be validated in other, larger studies, these results could be indicative for parent-counseling protocols. Developmental perspectives and advice may be profile-dependent. For example, children with below average language scores in combination with behavioural problems (profile 2 children) might have a worse prognosis regarding language outcome at school-age, than children with below average language scores but no behavioural problems (profile 3 children). In addition, if our preliminary results can be validated in further studies, these could lead to more appropriate early intervention as well. For example, children with profile 2 with detoriated language development and increased attention problems over time might benefit from behavioural enhancing intervention or intervention such as Cogmed®, i.e. a validated method that improves working memory and attention (45).

Conclusions

In conclusion, our preliminary study demonstrated that a multidisciplinary, profile-oriented approach may be relevant in VPT children to improve parent counseling and to enable early intervention and targeted treatment for those who are truly at risk. It should not be expected that high performers at age 2 continue to maintain their favorable development without further follow-up or treatment. Besides, behavioural problems at infant age appear to negatively impact language development, and delayed auditory nerve function at age 2 suggests a 'slow start' in language development followed by a catch up.

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Language functions deserve more attention in follow-up of

Language and brain structures in preterm children: A systematic review

Neurodevelopmental profiles preterms

Auditory maturation preterm

Lateralization in very preterm children

Narrative retelling in preterm born children.

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

Auditory maturation

Language functions deserve

brain

Narrative retelling in preterm

Language functions deserve more attention in follow

Neurodevelopmental profiles of very preterms

Chapter 9

Discussion, Synthesis and Future Perspectives

Discussion, Synthesis and Future Perspectives

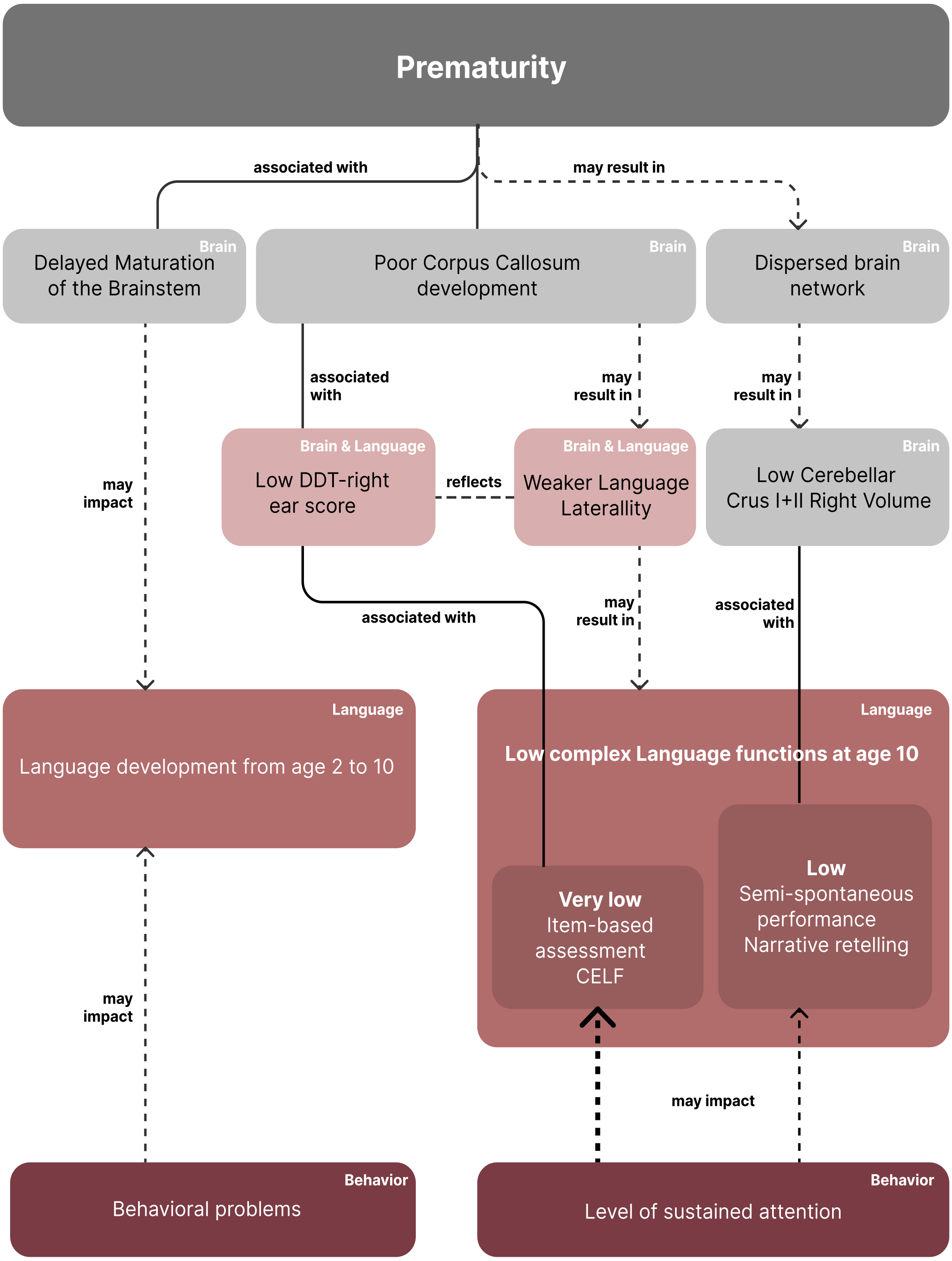
This thesis adds to the literature by extensively describing VPT children's long-term language development and its relationship with atypical brain development. Chapter 9 combines the results of the previous chapters and discusses new insights and hypotheses. Future perspectives, clinical implications and recommendations regarding the follow-up of VPT children will be presented, with the purpose of enhancing evidence-based practice. A synthesis model of the main results of this thesis are also presented in Figure 1.

Language development in school-age VPT children

The main purpose of this thesis is to describe the language difficulties that are typical for VPT children. Language functions are crucial to children's academic and societal achievements and to communication in everyday life. Language is required for many activities - reading books, watching television, listening to teacher instructions, making assignments at school, and all social activities. Furthermore, language proficiency plays a decisive role in the formation of relationships with caregiver and peers and in career success later on in life. Therefore, language difficulties severely impact children's development on various levels and, thus, their quality of life. Moreover, poor language functions at a young age have been shown to be a risk factor for several developmental disorders, such as autism spectrum disorders. Language proficiency is therefore very important for the long-term outcome of VPT children.

At age 10, VPT's complex language functions are more affected than their simple language functions, as shown in chapter 4. The core language score of the CELF (i.e. the mean of several item-based language tasks reflecting different language competencies) was significantly lower than scores on a relatively simple receptive vocabulary test, compared to the age-matched norm group. CELF scores were also lower than verbal IQ scores, which reflect cognitive tasks that require language. A more detailed analysis of complex language performances was made in chapter 5 since only the more complex language tasks appear to show the language difficulties of VPT children adequately. This chapter compares language test scores of the CELF with narrative retelling scores. Narrative retelling skills reflect the integration of semantics, morphology, syntax, and pragmatics in a semi-spontaneous, semi-structured setting. Narrative retelling scores estimate daily, spontaneous communication problems more adequately than language test scores of the CELF. It was therefore expected that narrative retelling performance would show the language difficulties of VPT children more clearly than traditional language test scores. Although both tasks showed significantly lower scores with VPT children than with term-born children, the narrative retelling scores of the VPT children were relatively high compared to their language test scores. To explain these results, chapters 4 and 5 discuss the role of attention skills in language functioning. We assume that the increased

Figure 1. Synthesis model of this thesis.



complexity of language tasks will require a higher level of sustained attention. Furthermore, it is known from the literature that VPT children show behavioral attention problems significantly more often than term-born children (1). A recent study also shows that children with language disorders show a significant association between language scores and sustained attention, while typically developing children do not (2). An item-based language assessment (e.g. the CELF) takes more time than a narrative retelling assessment and requires numerous items and turn taking shifts. These traditional language tests therefore might be more impacted by attention skills than the short narrative retelling task. In chapter 4 the association between the core score of the CELF and the attention problem score of the Child Behavior Checklist (CBCL) is tested. The CBCL is a parental questionnaire containing an attention problem score reflecting the judgment of parents on several behaviors such as "can't sit still" which need to be judged with 0 (not true), 1 (sometimes true) or 2(very/often true). The result in chapter 4 shows no association between the core score of the CELF and the attention problem score of the CBCL. This would imply that VPT children's language problems were not impacted by attention problems. However, an increased attention problem score on the CBCL questionnaire does not necessarily reflect a weaker level of sustained attention, unless it results in problem behaviors. If language test scores are impacted by a weaker level of sustained attention in VPT children, it implies that these test scores might overestimate language problems in VPT children in everyday communicative situations. On the other hand, language and attention are often intertwined in real-life, predominantly academic, settings. In the classroom, for example, sustained attention and dual attention are required while processing the language input of the teacher, making assignments, discussing with peers, asking questions etc. Therefore, traditional language assessments may predominantly show the language problems in an academic setting, where they were found to be significant. To reveal spontaneous language proficiency of VPT children, assessing narrative (re)telling performance may be useful in addition to traditional language assessments.

A comparison of language test scores and narrative retelling scores also show that VPT children with high language test scores use relatively lengthy sentences in narrative retelling. Full-term children with high language scores, on the other hand, use relatively short sentences. This comparison suggests that VPT children may be less able to use semantically dense sentences to express their ideas in a compact careful way (3). However, despite these differences between language test scores and narrative retelling outcomes, both outcomes were significantly lower than those of full-term children, perhaps suggesting a common neurological cause.

Underlying neuropathology

Language difficulties of VPT children are most likely a consequence of atypical neurological development (4-6). VPT children are born before or during the third trimester of pregnancy, which is a crucial phase for brain maturation. VPT children with focal brain lesions (e.g. hemorrhages) or more global brain injuries (e.g. periventricular leukomalacia) as a complication of preterm birth are at risk for developing severe neurodevelopmental impairments. However, the relatively healthy study group that was examined in this thesis did not have overt lesions as seen on routine imaging. They may therefore show the atypical development of the brain due to premature birth, independent of specific lesions or handicaps occurring in the postnatal phase. The results of this thesis contribute to the hypothesis that preterm birth results not only in a higher risk of illness and overt focal and/or global brain lesions, it also appears to result in atypical, unfavorable brain development, resulting in unfavorable language development, as has also been suggested by Volpe (5).

The systematic review in chapter 3 shows an overview of the relationships between language functions and brain volume. Specifically, it shows the importance of measuring (grey matter) volumes of smaller brain regions and their (white matter) connections in relation with language functions. Chapter 6 describes the relationship between semantic language functions, as assessed with a narrative retelling task, and grey matter volume of the cerebellar lobule Crus I+II of the right hemisphere. This significant association suggests that specific smaller volumetric parts of the brain of VPT children are crucially involved in language processing, while the cerebellum as a whole is not. We also explored the impact of hand preference on this relationship, which appears to be specifically important for syntactic language scores in a narrative retelling task. Only right-handed VPT children showed a significant positive association between grey matter volume of right Crus I+II and the syntactic score. Although we did not assess hand preference extensively, this result suggests that hand preference may interfere with language lateralization and with language functions in VPT children. Our preliminary results of the relationship between hand preference and language functions might suggest that left-handed VPT children have a different, less lateralized, brain organization, which may also impact the processing of language.

The model presented in chapter 7 continues on this subject, speculating that atypical language laterality in the brain may impact language functions of school-age VPT children. It is known from the literature that VPT children have smaller CC volumes (7, 8), which may be related to adverse neurodevelopmental outcome (9). The results of chapter 7 support the hypothesis that VPT children with poor language scores at the age of 10 may have had a poorly developed corpus callosum, leading to less lateralized language organization. A less lateralized brain may partly explain their language problems at school ages. From the literature it is known that hand preference may be associated with language lateralization (10). It has also been known that non-right-handedness is more common in VPT children, which was also the case in our study group (22%). Furthermore, results on the dichotic listening test showed that hand preference was associated with laterality. In contrast to the typically found right ear advantage in a dichotic listening test, left-handed VPT children were found to have equal scores for right and left ears. These equal scores for left-handed VPT children also suggest an alternative brain organization. It remains unclear, however, whether their brain organization is more bilateral or more contra-hemispherical and whether their atypical brain development results in decreased function. In full-term children it is also still unknown what exactly causes left-handedness and how it affects functions such as language. Both advantages and disadvantages have been described (11), which again shows the complexity of brain laterality.

The corpus callosum was shown to have a crucial role in language laterality and may therefore also be associated with language functioning (chapter 3 and 7). A weaker interhemispheric connection during childhood may also impact cognitive processing more generally. Evidence for both decreased inhibitory functioning and decreased excitatory functioning of the corpus callosum has been described (12). Both types of functioning may also influence language function. In daily life language tasks 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. Weaker interhemispheric connections may therefore diminish language functioning in such communicative situations.

Another hypothesis that could explain the weaker language functioning of VPT children: the brain organization of VPT children has relatively few expert regions. If so, VPT children have more, and smaller regions that need to be activated for the same function. If this hypothesis could be validated in future research, it would suggest that VPT children need to appeal to more and smaller regions than full term peers. This may be less efficient, costing more mental strain. VPT children may therefore not sustain a level of activation as high as full-term children can. This might also clarify the poorer scores of VPT children on more extensive, complex assessments. It may also explain their relatively good performance on simpler or shorter tasks or tasks that require less sustained attention. This hypothesis also suggests that microstructures are crucial to study in this specific patient group. Moreover, if VPT children have a more dispersed brain network, their brain organizations might also be more variable. This would suggest that relationships between brain and language functions are more complex in VPT children than in full term peers. It might also explain the complex and sometimes contradictory outcomes of the review in chapter 3, which addresses the relationships between language outcome and macro- and microstructures of the brain. A lack of association between function and brain outcome in VPT children, compared to a significant association in full-term children, might also provide evidence for a more dispersed brain network in VPT children. This argument was also used by Bruckert et al. as an explanation for the significant association they found between reading ability and white matter pathways in full term children, that was not found in VPT children (13).

Multidisciplinary profiles

As suggested in chapter 8, a multidisciplinary, patient-oriented approach would be valuable for understanding and predicting the development of VPT children. The developmental problems of VPT children are thought to be caused by atypical brain development (4, 6). Therefore, problems in cognitive, behavioral and language functioning, executive functions, and auditory processing may all have the same common cause and might also mutually affect each other. Therefore, a focus on the individual VPT child with its variety of neurodevelopmental difficulties is important, rather than focusing on a specific domain of interest.

More specifically, the multidisciplinary approach of chapter 8 showed that delayed auditory brainstem responses might be a sign of delayed, but not disordered neurodevelopment. One of the four neurodevelopmental profiles of VPT children described in chapter 8 (profile 3) showed mild neurodevelopmental delay and delayed auditory nerve functions at the age of 2, but these children had caught up on their neurocognitive outcome at the age of 10. Hence, as also suggested in chapter 2, auditory brainstem measurements may provide relevant outcome measures at a young age. In individual, isolated measurements the predictive value may be small, but in a multidisciplinary model with several neurocognitive measurements an adequate prediction of neurodevelopmental trajectory might be attained.

The longitudinal approach of chapter 8 also showed an interesting developmental difference between male and female VPT children. In previous research, male sex has repeatedly been described as a risk factor for language difficulties. Several studies have shown boys to have lower neurocognitive scores than girls (14-16). In our group of VPT children, boys also performed worse than girls at the age of 2, specifically on receptive language outcome. However, the results discussed in chapter 8, suggest that boys, more often than girls, have a neurodevelopmental profile with a catch-up trajectory, which is in accordance with results of Doyle et al. (17). Moreover, girls had diminishing receptive language outcomes at the age of 10, resulting in equal receptive language outcomes for boys and girls at age 10. Therefore, boys may have a "slow to warm up" development, while girls show a "head start", but do not maintain this more advanced development when they reach school age. Future research should indicate whether this difference in development between boys and girls can be validated.

Directions for future research

Recommendations for future research regarding: Attention problems and language functions; microstructures of the brain; hand preference and laterality; electrophysiological measurements; a multidisciplinary approach; patient reported outcome; and treatment will be discussed in turn.

Attention problems and language functions

We recommend further studies on the association between language functions and attention problems in VPT children. Results of such studies would help researchers and clinicians better understand how attention problems affect several language assessments, as discussed in chapters 4 and 5. Besides, other functions, such as executive function and auditory processing might also influence language scores. How are these functions related to language in VPT children? In VPT children the interactions between several neurocognitive functions may be important because atypical development of these functions is probably a consequence of atypical brain development due to preterm birth. Based on two of our main study results, I think that the underlying cause of language difficulties may be different for VPT children than for full-term children. First, because of the opposite associations between narrative and language test scores for full term and VPT children (chapter 5). Second, because of the significant association between dichotic listening and language in VPT children, which was not found in full term peers (chapter 7). It might be useful to compare the neurodevelopmental outcomes of VPT children to those of full-term children with specific language impairments so as to study the underlying cause of the language problems more adequately.

Microstructures of the brain

Since the atypical brain development of VPT children without overt brain damage is complex and subtle (chapter 3, 6 and 7), studying neurological microstructures in VPT children is highly recommended. Further study on why some specific brain structures appear to be related to language functions would also be useful. We hypothesized that VPT children might have a more dispersed brain network with less expert regions than full term children. Therefore, connectome research (i.e. mapping of neural connections) may be a promising technique for future research in relation to VPT children's language functions. In addition, it could also be relevant to study whether there may also be advantages to such a dispersed brain organization: are there positive effects of activating more, smaller regions compared to activating larger expert regions or are there adverse effects only?

Hand preference and laterality

We recommend assessing hand preference extensively when studying language laterality in VPT children, as it was shown to be a relevant aspect of language functions in these children in chapters 6 and 7. In the current study, children were asked only if they were right- or left-handed. However, children's handedness may also be mixed (i.e. a different hand for a different task) or ambidextrous (i.e. both hands with equal skills). Including these options may show important differences in laterality. In future research, hand preference should be assessed extensively. Hand preference and language functions are both related to atypical lateralization, but how are they related more precisely in VPT children? Is there a common cause or is there a causal relationship? Also, are language functions of VPT children associated with other lateralized functions, such as specific motor skills and emotionality? The role of the corpus callosum is expected to be an important consideration in future research on language functions and language lateralization.

Electrophysiological measurements

Chapters 2 and 8 both showed the potential value of electrophysiological measurements such as auditory brainstem responses in the early detection of delayed maturation. Data from the measurement of auditory event related potentials (aERPs) may provide information about the developmental path of language functions. aERPs of the study group in this thesis had already been measured, but their analyses proved to be difficult because of several technical challenges. However, for VPT children the technique of aERP is nonetheless promising since it is non-invasive, can be used with babies, and provides objective, functional information about the neurological processes underlying language functions.

A multidisciplinary approach

In future examinations of neurodevelopmental functions of VPT children, we recommend using the multidisciplinary approach described in chapter 8. If this approach can be validated in future research with larger cohorts, it may cause a change in clinical practice. Instead of assessing and describing isolated outcomes, several neurodevelopmental outcomes can be combined to provide a multidisciplinary, person-oriented profile. It might also be interesting to develop and test a tool to support clinicians during follow-up assessments and consultations, in order to provide an individualized, evidence-based prediction of the child's cognitive and language development. Such a tool should contain several neurodevelopmental parameters and norms for VPT and full-term children. Multidisciplinary test results of an individual child should be the input and the optimal neurodevelopmental profile and corresponding prognosis should be the output. Even corresponding advice, parent counselling or treatment options may be linked to the individualized profile.

Patient reported outcome

We recommend that valid and reliable patient reported outcome measures (PROMs) be developed through future research. The relatively good scores on narrative retelling compared to language test scores (chapter 5) showed that language scores from a test setting may not adequately reflect communication problems in everyday life. A communicative participation PROM will significantly improve future studies on the language functions of VPT children. This outcome measure will provide knowledge about the communication problems that children experience in everyday situations, including social activities and classroom situations. A PROM on the feelings and thoughts about communication situations would also be relevant to study: do VPT children experience a high level of mental strain during communicative interaction? Lastly, the judgements of interaction partners would be interesting to include in future research. In clinical practice we already ask parents to judge the child's communication in everyday life, but this PROM needs to be validated as well. An item bank may be helpful to structurally assess communication PROMs.

Treatment

Last, but not least, validating treatment options should be the subject of future research.

Parent counseling might be specifically helpful for relatively high performers by age 2. Since we have shown in chapter 8 that the development of these children may deteriorate during childhood, clinicians may use these research results and explain the favorable results with caution. Parent counseling is expected to be useful in early follow-up, but its effect needs to be studied.

Also, direct treatment options may be effective for a subgroup of VPT children. Future research may provide specific treatment indications by studying the effects of therapy programs. Currently, the effect of early parent-based intervention in two-year-old VPT children with speech sound disorders is being studied in a randomized controlled trial at Sophia's Children's Hospital. This research will provide specific information about the effect of speech therapy. Randomized controlled trials are necessary for developing evidence-based therapy protocols. The effect of direct language treatment in VPT children should be studied in future research as well.

In addition, the effect of indirect treatment, focusing on the parents, may also be a relevant future research topic. Poor language performance at school age was associated with parents' poor vocabulary knowledge (chapter 4). Parental language may be important in the child's long term language development since it provides the main contribution to children's language input and language input is the main basis of children's language development (18). Therefore, parental language functions, crucial for all children, are especially important for VPT children. Poor parental vocabulary may prove to be a risk factor for poor language outcome in the child and may therefore be an indicator for parental treatment. Parents with low vocabulary knowledge may profit from treatment programs that indirectly and inexpensively teach parents co-therapist skills. Offering parental treatment when the child is still young will optimize the language input of the child. An example of such a parental course is the Hanen program for parents (19), where parents learn how to create language rich environments in order to facilitate their child's (language) development. If future research can validate the use of these indirect treatments for VPT children, it will most likely be effective if provided when the child is still young.

Directions for clinical follow-up of VPT children

As a result of the current research, we have several recommendations for the follow-up protocol of VPT children in the clinical practice, as follows.

Follow-up at age 2

In most European countries, the two-year follow-up is considered an important milestone. Clinicians identify children who are at risk and need treatment or monitoring. The NICE guideline, published in 2017, emphasizes the assessment of cognitive, language, hearing and behavioral functioning (20, 21). However, language functions are not yet routinely assessed at follow-up in most European hospitals. Based on the results of this thesis, we suggest routinely screening for language difficulties at the age of 2, with a screening tool such as the Early Language Scale (ELS) (22). A screening score below the minimum language norms would indicate further language assessment. Besides, this thesis clearly indicates extensive language assessment on the basis verbal IQ scores. VPT children with low average verbal IQ scores (i.e. quotient score of 85-92) were found to be at risk for significantly lower language test scores (chapter 4). Therefore, low verbal IQ scores may also indicate further assessment by a speech-language pathologist, who can assess, analyze and interpret language functions. Not only academic language functions, but also more spontaneous language use can be assessed, for example through narrative (re)telling tasks. Moreover, adequate language assessment may lead to specific indications for speech and language therapy.

Screening at age 4

We also recommend screening for language difficulties later on in childhood (23). Screening at the age of 4, prior to starting school, might be helpful. Additionally, language assessment at the age of 4 may also be valuable, for four reasons:

- Language functions can be assessed more reliably at 4 than at 2 since children are then able to focus better on a language test.
- Test results may lead to more individualized, direct therapy suggestions.
- Developmental trajectories differ between 2 and 10 years of age (chapter 8). An additional and preliminary analysis of the language scores at the age of 4 suggested that outcome at age 4 may provide better indications for later development.
- From clinical experience it appeared that parents do not always appreciate additional assessments at the age of 2. The language assessment adds to the many different hospital visits in the first 2 years of their child's life. Since language development of children around the age of 2 varies widely, parents often believe that their child needs some more time to develop spontaneously. They therefore do not always feel the urge to start direct treatment at that moment. Language assessment around the age of 4 years may evoke a more motivated parental attitude, which may lead to more successful treatment if needed. However, screening at the age of 2, followed by an

assessment for at risk children, is also important, because of the expected favorable effect of treatment at a young age.

Monitoring until adulthood

Improved perinatal care significantly reduced mortality rates in infants born preterm, which resulted in increasing interest in the long-term neurodevelopmental outcome of VPT children. How do these children function in school? Can they participate in society? What professions do they practice? What is their quality of life? Monitoring of these more general quality of life measures until adulthood may be relevant in addition to the neurodevelopmental screening and assessments. To restrict the effort requiring such monitoring, online questionnaires could be used instead of organizing appointments at the hospital. Monitoring with questionnaires may lower the threshold for parents and children to ask for help when the child is having problems in daily life. Besides, a large amount of data about this patient group can be collected, which can be the basis of future healthcare improvement.

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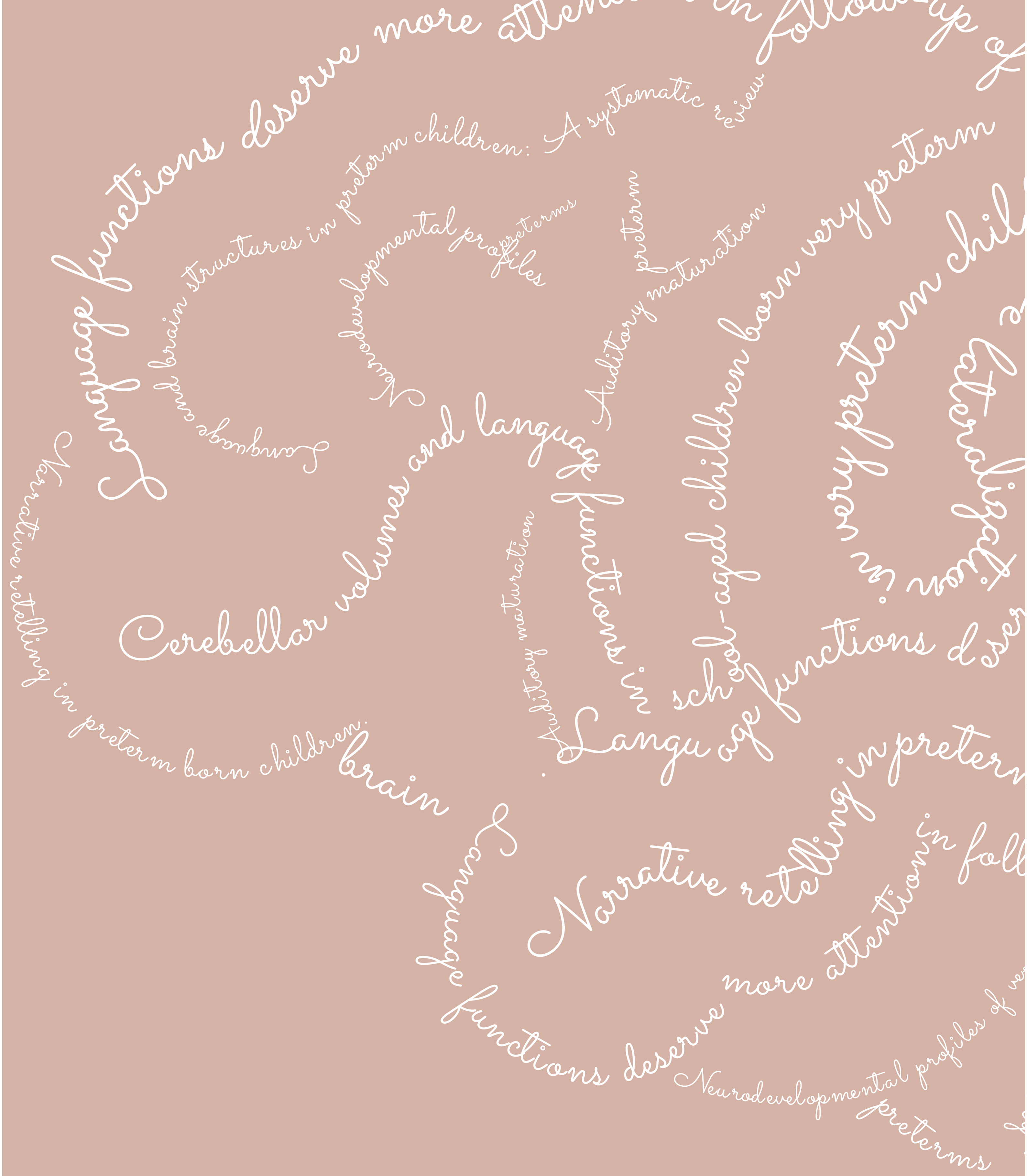
Language functions deserve more attention in follow-up of
Language and brain structures in preterm children: A systematic review
Neurodevelopmental profiles preterms
Auditory maturation preterm
Cerebellar volumes and language functions in school-aged children born very preterm
Lateralization in very preterm children
Narrative retelling in preterm born children.
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Appendices

Summary

Summary

Children born very preterm (VPT, i.e. born <32 weeks gestation) represent more than 1% of all neonates. Last decades, survival rates have increased thanks to technological advances and combined efforts of obstetricians and neonatologists. However, survivors remain at risk for adverse neurodevelopmental outcomes later in life. Approximately 40% of VPT children without major handicaps still have language problems at school age. This is alarming since language is crucial for academic and social achievements.

This thesis is dedicated to the extensive study of the language functions of VPT children and the underlying neurological process of the language problems which these children experience. Chapter 1 introduces and motivates this thesis. It describes the complexity of language and its development throughout childhood. It provides the fundamentals of preterm birth and its impact on brain development. The most important biomedical and social risk factors for adverse neurodevelopmental outcome in VPT children are presented and the current standards regarding the long-term follow-up of VPT children in clinical practice are described.

Chapter 2 of this thesis studies the early maturation of the brain in preterms since this may be predictive for adverse neurodevelopmental outcome. In a meta-analysis of 16 studies the early maturation of normal hearing preterm and term born children are compared by measuring auditory brainstem responses at infant age. Results of these studies are combined since individual differences in these kinds of measurements are very small, but larger sample sizes may show group differences. The meta-analysis shows that auditory stimuli arrive at the brainstem with a significant delay. The delay predominantly occurs in the last part of the route: from the auditory nerve towards and into the auditory brainstem. This suggests atypical maturation of the brainstem in normal hearing preterm born infants. Both smaller gestational age and more severe consequences of preterm birth are shown to negatively affect maturation of the auditory brainstem, which may influence later development.

Chapter 3 also presents results of the existing literature as a basis for the following chapters and describes the relations between language and brain on later age. The chapter shows a systematic review of 23 studies, each associating a language function to the volume of a brain structure in school-aged preterm and at term born children. This matrix of results differentiates 3 sorts of language measures and 7 often used brain measures. The relations appeared to be complex and ambiguous. Not one single brain area appeared to be responsible for language problems, but several regions and their connections seem to be important to language functioning. However, several studies showed the corpus callosum (i.e. the connection between hemispheres) to be positively associated with oral language functions.

Chapter 4-8 describe the results of a longitudinal study of a group of VPT children, born at Erasmus MC – Sophia's Children's Hospital. Chapter 4 compares results on simple and more complex language functions with cognitive functions, behavioral problems and executive functioning of 10 year old VPT children. It shows that VPT children score significantly lower on complex language tasks, combining several language components such as grammar and semantics, than on a more simple receptive vocabulary task. It also shows that these complex language scores are significantly lower than the verbal IQ scores of these children. At the same time, this chapter also describes that verbal IQ and complex language scores were significantly positively associated. This result is important to the clinical setting since it is currently not conventional in Europe to structurally assess language functions in follow up. Verbal IQ which is often structurally assessed, does not reflect absolute language scores adequately. Clinicians should be aware of the possibly significantly lower complex language functions. This chapter also shows that the vocabulary level of the parent is positively associated with the complex language functions of their child at school age.

Chapter 5 presents a more detailed analysis on complex language functions of VPT children comparing an item based complex language test with a semi spontaneous narrative retelling task. It shows that VPT children score significantly lower than term born children on both complex language tests. However, the difference is much smaller for the narrative retelling task. A narrative task is often seen as an adequate reflection of spontaneous language use and an item-based task is assumed to reflect academic language use more adequately, requiring better sustained attention. This chapter suggests that the often low sustained attention skills of VPT children may negatively impact the item-based language scores more than they affect a narrative retelling task. The chapter concludes that spontaneous language tasks may be an important addition in the language assessment battery for VPT children since sustained attention might affect this task.

Chapter 6 falls back on the relation between language performance and underlying brain structures. From literature it is known that specific lobules of the cerebellum may be associated with semantic language functions. However, lobular volumes were never associated with semantic language functions in VPT children before, but up till now only total cerebellar volume was used. Therefore, this chapter describes the relationship between volume of Crus I+II of the right hemisphere and a semantic language measure from the narrative retelling task. A significant positive association is described, while no significant association was found between total cerebellar volume and the semantic language measure. This chapter, therefore, concludes that smaller cerebellar volumes may be crucial to specific language functions, but total cerebellar volume is not.

Chapter 7 describes the relation between language and brain in VPT children differently, centralizing the role of language lateralization. Typically, language lateralizes to the left hemispheres in the first years of life. The corpus callosum plays an important role in this lateralization process. From the literature it is known that VPT children on average have a smaller corpus callosum than term born children. Chapter 7 describes the significant association between the corpus callosum and a score on the functional dichotic listening task. In the dichotic listening test digits were presented to the left and right ear simultaneously. Typically, children recall digits presented to the right ear better because of the direct connection between the right ear and the left cerebral hemisphere. This is referred to as the right ear advantage, reflecting adequate language lateralization to the left hemisphere. In VPT children the right ear score is significantly lower and associated with the corpus callosum on one side and with language performance on the other side. Together these results support the hypothesis that VPT children have weaker lateralized language functions with weaker language performance at school age as a result.

Finally, chapter 8 presents a novel, multidisciplinary way of studying the neurocognitive development of VPT children in two parts. Results on language, cognitive, and behavioral performance and auditory maturation at the age of 2 were combined using factor and cluster analysis. This has resulted in 4 distinctive neurocognitive profiles of VPT children. The development of these 4 profiles is described until the age of 10 years. It shows that the relatively high performers at age 2 have a decreasing developmental path up until the age of 10 on all different outcomes. Furthermore, a delayed auditory maturation might predict a slow to warm up development, while early behavioral problems might predict less potential to grow and an unfavorable development. This chapter describes the development of these profiles in the relatively small cohort of the current study, but it also recommends using this profile-oriented approach more often in larger cohorts in future research.

Chapter 9 concludes with a general discussion and syntheses of all results of this thesis. It shows a strong, but complex relation between atypical brain development due to preterm birth and language difficulties at the age of 10. The found relations between language development and the corpus callosum and specific smaller brain regions provide new insights for further research. Future studies on language performance of preterm children may need to focus on the language lateralization process and may need to study the brain on a microstructural level. Furthermore, this thesis shows that language problems of 10-year-old preterm children specifically occur during more complex language tasks, combining several language domains (such as grammar, semantics and pragmatics) but not when only vocabulary knowledge is assessed. The combination of performing such a complex language task and sustaining their attention to it relatively long is very difficult for very preterm born children. However, this combination is crucial in academic setting. Therefore, it is very important to assess language functions in the neonatal follow-up of very preterm born children more adequately, with a multidisciplinary view and monitor the communicative problems of these children up until adulthood.

Samenvatting

Samenvatting

Ruim 1% van alle geboortes vindt veel te vroeg plaats (vóór 32 weken zwangerschap). In de afgelopen decennia zijn de overlevingskansen van deze kinderen flink gestegen dankzij technologische verbeteringen en de inzet van neonatologen en verloskundigen. Deze kinderen hebben echter wel een verhoogd risico op een ongunstige lange termijn ontwikkeling op verschillende gebieden. Ruim 40% van de veel te vroeg geboren kinderen zonder grote handicaps heeft op schoolleeftijd nog steeds taalproblemen. Dit is alarmerend, aangezien taal cruciaal is voor zowel schoolse als sociale prestaties.

Dit proefschrift richt zich op het uitgebreid onderzoeken van de taalvaardigheden van schoolgaande veel te vroeg geboren kinderen en het blootleggen van de onderliggende neurologische processen. In hoofdstuk 1 wordt dit onderwerp uitgebreid geïntroduceerd en wordt de motivatie voor de studie uiteengezet. Het beschrijft de complexiteit van taal als fenomeen en van de ontwikkeling van taalfuncties bij kinderen. Het verstrekt achtergrondinformatie over prematuriteit en de invloed die vroeggeboorte heeft op de ontwikkeling van het brein. Het beschrijft de belangrijkste biomedische en sociale risicofactoren voor ontwikkelingsproblemen en het huidige protocol rondom de lange termijn follow-up van prematuren in de klinische praktijk.

Hoofdstuk 2 van deze thesis onderzoekt de vroege rijping van het brein bij prematuren omdat dit voorspellend zou kunnen zijn voor een ongunstige neurocognitieve ontwikkeling. In een meta-analyse van 16 studies wordt de vroege rijping van normaalhorende te vroeg en op tijd geboren kinderen vergeleken door auditieve hersenstam responsies te meten vlak na de geboorte. De resultaten van deze studies worden samen genomen omdat individuele verschillen in dit soort metingen erg klein zijn, maar grotere groepen meer duidelijkheid geven over eventuele groepsverschillen. De meta-analyse laat zien dat auditieve stimuli bij prematuren vertraagd in de hersenstam aankomen. De vertraging vindt vooral plaats in het laatste stukje op de route: van de gehoorzenuw tot in de hersenstam. Dit suggereert een vertraagde rijping van de hersenstam in prematuren. Zowel een kortere zwangerschapsduur als een ernstiger ziekteverloop in de postnatale fase hebben een negatieve impact op deze rijping, wat latere ontwikkeling zou kunnen beïnvloeden.

Hoofdstuk 3 presenteert ook resultaten van bestaande studies als basis voor de hoofdtukken die volgen en beschrijft de relaties tussen taal en brein op latere leeftijd. Het hoofdstuk toont een systematisch overzicht van 23 studies die elk een relatie tussen een taalvaardigheid en het volume van een breinstructuur hebben vergeleken tussen premature en op tijd geboren kinderen op school leeftijd. In de matrix van uitkomsten wordt onderscheid gemaakt tussen 3 soorten taalmetingen en 7 vaak gebruikte breinmetingen. De relaties geven geen eenduidig beeld en blijken zeer complex. Niet een enkel gebied in het brein lijkt verantwoordelijk voor afwijkende taalontwikkeling, maar verschillende gebieden en hun connecties lijken van belang voor taalontwikkeling. Wel bleek het corpus callosum (de verbindingsbalk tussen de hersenhelften) in verscheidene studies positief geassocieerd met gesroken taalmaten.

De hoofdstukken 4 t/m 8 beschrijven de resultaten van een longitudinale studie bij een groep van veel te vroeg geboren kinderen, geboren in het Erasmus MC -Sophia Kinderziekenhuis. Hoofdstuk 4 vergelijkt resultaten op simpele en complexe taaltaken met intelligentiescores, gedragsproblemen en executieve functiescores van 10-jarige prematuren. Het laat zien dat prematuren significant lager scoren op complexe taaltaken, waarbij verschillende taalaspecten zoals grammatica en semantiek gecombineerd moeten worden, dan op een simpelere passieve woordenschat taak. Het laat ook zien dat hun complexe taalscores veel lager zijn dan hun verbaal IQ. Tegelijkertijd wordt beschreven dat verbaal IQ en de gebruikte complexe taaltaak wel sterk geassocieerd zijn. Dit resultaat is van belang voor het werkveld omdat het in Europa nu niet gebruikelijk is om taal structureel te meten in de follow-up. Een verbaal IQ, dat vaak wel structureel getest wordt, is geen goede reflectie van de absolute taalscores. Clinici moeten daarom bedacht zijn op veel lagere taalfuncties ten opzichte van het verbale IQ of van de woordenschat. Ook werd gezien dat het woordenschatniveau van de ouder voorspellend is voor de complexe taalvaardigheden van hun kind.

Hoofdstuk 5 gaat dieper in op de complexe taalfuncties van prematuren en vergelijkt een op items gebaseerde taaltest met een semi-spontane naverteltaak. Het laat zien dat prematuren significant lager scoren dan op tijd geboren kinderen op beide complexe taaltaken, maar dat dit verschil kleiner is in de naverteltaak. Een naverteltaak wordt gezien als een betere afspiegeling van spontaan taalgebruik en een op items gebaseerde test reflecteert meer de taalfuncties die nodig zijn in een academische setting, waarvoor vastgehouden aandacht nodig is. Dit hoofdstuk suggereert dat de vaak slechtere vastgehouden aandacht van prematuren een negatieve impact kan hebben op een op items gebaseerde taaltaak, meer dan het een naverteltaak zal beïnvloeden. Er wordt geconcludeerd dat spontane taaltaken een belangrijke aanvulling kunnen zijn op de diagnostiek van taalproblemen bij prematuren omdat een verminderde vastgehouden aandacht hierin een minder grote rol zal spelen.

Hoofdstuk 6 grijpt terug op de relatie tussen taalvaardigheden en onderliggende breinstructuren. Uit de literatuur is eerder gebleken dat specifieke lobuli (kwabben) van het cerebellum (de kleine hersenen) geassocieerd zijn met semantische taalfuncties. Echter werd nog niet eerder gekeken naar specifieke volumes van deze lobuli in relatie tot taalfuncties in prematuren, maar werd tot nu toe alleen gekeken naar het totaal volume van het cerebellum. Daarom beschrijft dit hoofdstuk de relatie tussen het volume van cerebellaire lobuli Crus I+II van de rechter hersenhelft en een semantische uitkomstmaat van de narratieve naverteltaak. Er wordt een significante positieve relatie beschreven tussen deze twee maten, terwijl er geen significante relatie wordt gezien tussen het totale cerebellaire volume en deze semantische taalmaat. Het hoofdstuk sluit daarom af met de boodschap dat kleinere cerebellaire volumes van belang lijken voor specifieke taalfuncties, maar het totale cerebellaire volume daar geen inzicht in geeft.

Hoofdstuk 7 onderzoekt de relatie tussen taal en het brein bij prematuren op een andere manier, waarin de rol van taallateralisatie centraal staat. Taalfuncties lateraliseren normaal gesproken in de eerste levensjaren naar de linker hersenhelft. Het corpus callosum speelt hierin waarschijnlijk een belangrijke rol. Uit de literatuur is bekend dat prematuren gemiddeld genomen een minder goed ontwikkeld corpus callosum hebben dan op tijd geboren kinderen. Hoofdstuk 7 beschrijft een significante associatie tussen het corpus callosum en een score op de functionele dichotische luistertaak. Bij zo'n dichotische luistertaak moeten getallen nagezegd worden die tegelijkertijd in het rechter en het linker oor worden aangeboden. Normaal gesproken worden de cijfers van het rechter oor sneller verwerkt door de directe verbinding met de linker hersenhelft. Dit wordt het rechteroorvoordeel genoemd, dat een goede lateralisatie van taalfuncties naar de linker hersenhelft reflecteert. Bij prematuren is de score van het rechteroor significant lager en geassocieerd met het corpus callosum enerzijds, en met taalscores anderzijds. Deze resultaten samen ondersteunen de hypothese dat taalfuncties bij prematuren slechter gelateraliseerd zijn naar de linker hersenhelft en dit een oorzaak zou kunnen zijn van de taalproblemen die prematuren hebben op schoolleeftijd.

Hoofdstuk 8 presenteert een nieuwe, multidisciplinaire manier van kijken naar de neurocognitieve ontwikkeling van prematuren. De taalscores, intelligentie scores, gedragsscores en auditieve rijpingsscores op de leeftijd van 2 jaar worden gecombineerd met een factor- en clusteranalyse en er worden 4 multidisciplinaire profielen van prematuren gedefinieerd. De ontwikkeling van deze 4 groepen van prematuren wordt beschreven tot op de leeftijd van 10 jaar. Hieruit blijkt dat de kinderen die op 2 jaar het beste uit kwamen een forse daling laten zien in hun scores op alle neurocognitieve gebieden. Verder lijkt een tragere auditieve rijping op 2 jaar mogelijk een slow to warm up ontwikkeling te betekenen, waar gedragsproblemen juist een zwakkere ontwikkeling zouden kunnen voorspellen. Dit hoofdstuk beschrijft deze ontwikkeling in het relatief kleine sample van de huidige studie, maar het beveelt vooral aan om cohorten van prematuren vaker op deze manier te bestuderen.

Hoofdstuk 9 besluit met een conclusie en synthese van alle resultaten van dit proefschrift samen. Hieruit blijkt dat er een sterk, maar complex verband is tussen atypische breinontwikkeling door vroeggeboorte en taalproblemen op 10-jarige leeftijd. De gevonden relaties tussen taalontwikkeling en het corpus callosum en juist kleine structuren van het brein geven nieuwe inzichten voor vervolgonderzoek. In toekomstige studies naar de taalontwikkeling van prematuren zal aandacht moeten zijn voor het lateralisatieproces en zal het brein op microstructureel niveau verder onderzocht moet worden. Dit proefschrift toont daarnaast aan dat de taalproblemen die te vroeg geboren kinderen op 10-jarige leeftijd hebben zich vooral uiten in taaltaken waarbij verschillende taaldomeinen (zoals grammatica, betekenis en pragmatiek) samen komen en niet wanneer bijvoorbeeld alleen de vocabulaire wordt getest. De combinatie van het uitvoeren van zo’n complexe taaltaak en het relatief lang vasthouden van hun aandacht ervoor is extra lastig voor te vroeg geboren kinderen. Een combinatie die in schoolse setting wel cruciaal is. Het is daarom van groot belang de taalfuncties van veel te vroeg geboren kinderen beter te onderzoeken binnen de neonatale follow-up, met een multidisciplinaire blik, en de communicatieve problemen van deze kinderen te monitoren tot aan de volwassen leeftijd.

PhD Portfolio

PhD Portfolio

Name PhD student:	Lottie Stipdonk
PhD period:	2016-2021
Erasmus MC department:	Otorhinolaryngology
Promotor:	Prof. Dr. R.J. Baatenburg de Jong
Co-promotors:	Dr. M.C.J.P. Franken
	Dr. J. Dudink

PhD Portfolio	Year	Workload ECTS
Training		
Utrecht Summer School: Neurocognitive Methods for Infant and Toddler Research	2015	2
BROK	2017	1,5
Research Integrity	2017	0,3
NIHES case-control studies	2017	0,7
Biomedical English Writing and Communication	2018	3
Presentations		
NVA symposium	2016	0,5
NVKNO symposium 2x	2016 and 2020	1
Treatment and Research Meeting Pediatric Psychology	2017	0,5
LNF symposium	2020	0,7
EAPS Paris, poster viewing 2x	2018 and 2020	0,8
EAPS Paris, poster discussion	2018	0,4
EAPS Barcelona, oral presentations 2x	2020	1,6
Research day ENT Erasmus MC	2019	0,5
Neonatal Neurology symposium	2019	0,5
WAP symposium Language and Brain	2020	0,5
Conferences		
Symposium Language and Hearing Center Amsterdam	2016	0,2
LNF symposium	2017	0,3
Symposium Diagnostics of speech disorders	2017	0,3
Support of different research internships of MA-students of Neuroscience and Cognition and Speech and Language Pathology students	2016-2020	

Over de auteur

Over de auteur

Lottie Stipdonk is geboren op 1 september 1987 in het kleine dorp Woubrugge, dichtbij Leiden. Zij behaalde haar eindexamen VWO aan het Ashram College te Alphen aan den Rijn in 2005 en begon met de bachelor Algemene Taalwetenschap aan de Universiteit van Amsterdam. Na het behalen van haar bachelor, startte zij met de master Language, Speech and Hearing Sciences (Logopediewetenschap) aan de Universiteit Utrecht. Zij combineerde dit in een schakeltraject met een verkorte HBO bachelor Logopedie om zo haar therapiebevoegdheid te halen en wetenschap en patiëntenzorg te kunnen combineren. Haar afstudeeronderzoek naar karaktereigenschappen bij jongeren die stotteren vond plaats in samenwerking met het Erasmus MC. Haar thesis resulteerde in haar eerste wetenschappelijk publicatie. Ze behaalde haar master in 2012, waarna zij startte als logopedist bij het Gehoor- en Spraakcentrum in het Erasmus MC. Gezien haar nadrukkelijke wens om klinische en wetenschappelijke taken te combineren, leverde zij aan verschillende onderzoeksprojecten een bijdrage als junior onderzoeker. Na het aanvragen van verschillende kleine en grotere subsidies kon zij in 2016 starten met haar promotieonderzoek dat leidde tot dit proefschrift. Binnen haar huidige werkzaamheden als logopedist en klinisch linguïst ontwikkelt zij zich, op wetenschappelijk en klinisch vlak, verder in de diagnostiek en behandeling van kinderen die stotteren.

Lottie woont samen met haar man, Jochem, en hun twee kinderen, Pippa (2016) en Olaf (2018), in de mooie binnenstad van Delft, waar zij dit jaar zullen verhuizen naar hun duurzame zelfbouwwoning.

Dankwoord

Dankwoord

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