The Identification of Early Neuroimaging Biomarkers of (Impaired) Language Development in Extremely and Very Preterm Children

Literature Review

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Abstract

Background. Prematurity is associated with a diverse range of neurodevelopmental sequelae. For instance, a premature birth can lead to language impairment. Various studies have investigated the language development of extremely and very preterm children. However, their language development has barely been correlated with brain characteristics, while brain abnormalities could have prognostic value for the identification of children at risk for a language delay. This scoping review aims to synthesize the current literature by providing an overview of studies which investigate neuroimaging biomarkers of impaired language development in extremely and very preterm children. This could stimulate the timely start of interventions that attenuate the negative impact of prematurity on language skills, when neuroplasticity is at its peak.

Methods. We selected a subset of articles by conducting an advanced PubMed search and screening their abstracts and titles. Studies were eligible for inclusion when the study consisted of a population of extremely or very preterm infants (≤32 weeks GA), the study used a neuroimaging method at term-equivalent age to measure brain abnormalities or specific parameters, the study reported at least one language outcome, and a correlational measure could be extracted that represented an association between brain and language. In total, 28 studies were included.

Results. The results were split between extremely and very preterm infants: seven studies were conducted on extremely preterm infants, while 21 studies examined very preterm infants. Overall, no major differences were found between the two groups. Most significant correlations between brain metrics and language were found for biomarkers from the categories brain morphometry and brain volumes. White matter had the most predictive power from all tissue types. Studies that adopted a novel approach by using an innovative neuroimaging method and/or multimodal research design were among the most successful ones in classifying preterm children at high or low risk for a language delay based on their brain features. The results were quite inconsistent for biomarkers from the categories structural abnormalities and white matter microstructure and connectivity.

Conclusion. Despite some inconsistency within the results, various neuroimaging biomarkers were discovered that have added value for the identification of infants with an increased risk for language impairment. Brain morphometric and volumetric biomarkers were the most promising, whereas biomarkers from the categories structural abnormalities and white matter microstructure and connectivity were not reliable enough. Further research is needed to confirm this. Future studies are advised to use stricter inclusion criteria for more selective data collection, to facilitate comparisons between included articles. Future studies should also focus on the potential of deep learning (multimodal) models and go beyond the golden standard MRI.

Keywords: brain morphometry, brain volume, prematurity, language development, neuroimaging, prognostic biomarker, prematurity, review, structural abnormalities, white matter integrity

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Plain Language Summary

A normal pregnancy takes around 37 to 40 weeks. Children who are born before or at 28 weeks are called extremely preterm, and children born before or at 32 weeks are called very preterm children. These children experience various problems in their life, which influence their physical and mental wellbeing. For example, a premature birth can lead to language impairment: many extremely and very preterm children experience a language delay. They could have trouble with grammar or are worse at comprehending sentences than their full-term peers (children who were not born premature).

It would be useful to know which preterm children will be at risk for a language deficit before they have reached the final stage of language acquisition, so that therapies can be started at a young age and children get the help they need. This will optimize children's outcomes. Therefore, the aim of this literature review was to look for early signs that could indicate a later language problem in extremely or very preterm children. This review focused on signs in the brain, which can be found with the help of imaging techniques. Therefore, these signs are called neuroimaging biomarkers. This review provided an overview of studies that were conducted on this topic.

These studies were searched for within the online database PubMed. The search term resulted in 255 articles. A total of 28 studies met the inclusion criteria. These 28 studies evaluated the predictive power of the brain for later language development in extremely or very preterm children.

Overall, the results showed that two types of brain markers could be reliably used to predict the later language development of extremely and very preterm children. The first one was brain morphometry. Brain morphometry provides information about the shape and size of different brain structures and/or brain regions. A specific type of measurements that can be derived from brain morphometry are volumes. Brain volumes represent the (3D) amount of brain tissue that is present in a specific structure or region. To illustrate, when brain morphometry represents a house, the cubic space of each room (brain region) would correspond with volume. Both types of neuroimaging biomarkers were fruitful for the identification of high-risk extremely or very preterm children. These children often had smaller volumes than children who had a decreased risk for a language deficit.

To conclude, two neuroimaging biomarkers appear to have sufficient prognostic potential for the identification of preterm children with an increased risk for language impairment (i.e., brain morphometry and brain volumes). This literature review described a broad range of neuroimaging studies, which resulted in a rich overview. While this large variety in studies was a strength, it also complicated the making of comparisons between studies and the drawing of general conclusions. Future studies are therefore recommended to use stricter inclusion criteria. It would also be useful to look into the benefits of artificial intelligence and machine learning, since studies that used these techniques were quite successful in finding extremely or very preterm children who were at an increased risk for language problems.

List of Abbreviations

Abbreviation	Definition
AD	Axial diffusivity
ADC	Apparent diffusion coefficient
aEEG	Amplitude-integrated electroencephalography
ANCOVA	Analysis of covariance
ANONT	Animal Naming and Object Naming Test
BSID	Bayley Scales of Infant and Toddler Development
CA	Corrected age
CELF	Clinical Evaluation of Language Fundamentals
COWAT	Controlled Oral Word Association Test
CSF	Cerebrospinal fluid
CT	Cortical thickness
DAS	Differential Ability Scales
DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
EEG	Electroencephalography
EPT	Extremely preterm
FA	Fractional anisotropy
fMRI	Functional magnetic resonance imaging
FT	Full-term
GA	Gestational age
GI	Gyrification index
IFS	Inferior frontal sulcus
IVH	Intraventricular hemorrhage
LF	Lateral fissure
MD	Mean diffusivity
MRI	Magnetic resonance imaging
NEPSY	Developmental Neuropsychological Assessment
NICU	Neonatal intensive care unit
PLIC	Posterior limb of the internal capsule
PMA	Post-menstrual age
RD	Radial diffusivity
rsfMRI	Resting-state functional magnetic resonance imaging
RSN	Resting-state network

SA	Surface area
SD	Sulcal depth
SGRT	Schonnel Graded Reading Test
SST	Schonnel Spelling Test
TEA	Term-equivalent age
VPT	Very preterm
WISC	Wechsler Intelligence Scale for Children
WJ	Woodcock Johnson Tests of Achievement
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
WRAT	Wide Range Achievement Test

1. Introduction

Worldwide, very preterm (VPT) children account for roughly 1% of all live births (Konzett et al., 2024; Larroque et al., 2004; Smith et al., 2009). These children are born before or at 32 weeks of gestation (Brydges et al., 2018; Trimarco et al., 2024): the weeks they spend outside the womb are critical for optimal brain maturation (Locke & Kanekar, 2022). Approximately 15% of all premature births occur before 32 weeks (VPT). Within this group, roughly 30% of VPT births take place before 28 weeks (Ohuma et al., 2023). Infants who are born before 28 weeks are called extremely preterm (EPT) children (Quinn et al., 2016). In this review, both EPT and VPT children will be investigated. However, the focus in this section lies on VPT children. This is because VPT children (born ≤32 weeks) also comprise EPT children (born <28 weeks). Furthermore, VPT and EPT children experience similar kinds of (long-term) adverse effects due to a premature birth (Jois, 2019; Song, 2023).

Prematurity is a critical global health issue, as it worldwide constitutes the primary cause of death in children under five years (Liu et al., 2016; Ream & Lehwald, 2018). The mortality rate in VPT children lies around 10%, mortality decreasing with increasing gestational age (GA) and birth weight (Seaton et al., 2023; Shah et al., 2016) Advanced medical care and enhanced medical knowledge have substantially increased the survival chances of preterm children (Barfield, 2018).

However, VPT children are still extremely vulnerable, since prematurity is associated with long-term neurological sequelae. In total, 29% of all VPT children are estimated to experience mild-to-severe neurodevelopmental impairments during or after the neonatal period, of which 32.4% are susceptible to a mild deficit and 24.6% to a severe deficit (Blencowe et al., 2013). These adverse outcomes include motor problems (such as cerebral palsy), cognitive delay, visual impairments and deafness. Such problems are usually already visible from a young age. At a later age, preterm children also often experience behavioral deficits (e.g., autism spectrum disorder or attention deficit hyperactivity disorder) and develop social-emotional and language problems (Aarnoudse-Moens et al., 2009; Jois, 2019; Kroll et al., 2017; Montagna et al., 2020; Sanchez et al., 2019). Eventually, all these neurodevelopmental morbidities can lead to academic underachievement, lower economic attainment, and worse life satisfaction, and they often result in lifelong disabilities (Hadaya & Nosarti, 2020; Jois, 2019; Kroll et al., 2017).

Persistent language problems are one of the biggest problems in preterm children, since approximately 45% of all VPT children show a moderate or severe language impairment (Stipdonk et al., 2018, 2020). A recent retrospective cohort study demonstrated that the language domain was most affected by prematurity compared with other domains (e.g., audition, motor function or vision): at 2 years of age, a substantial proportion of all VPT children (18.6%) did not reach the linguistic milestones set for that age. Fewer VPT children experienced delays in motor function (7.3%), had visual impairments (4.5%) or needed auditory prosthesis/cochlear implant (1.1%). Moreover, 13.6% of all VPT children had some form of speech therapy (Pissara et al., 2023).

1.1. Impaired Language Development in Very Preterm Children

Language is a complex phenomenon and made up of several components, namely phonology (speech sounds), morphology (words), syntax (grammar), semantics (meaning) and pragmatics (social context) (Levy et al., 2021). Language development begins even before birth, since the auditory system of the fetus is already formed by 25 weeks of gestation. At 30 weeks of gestation, the fetus is even able to discriminate speech sounds and react to auditory stimuli. These speech signals shape the perceptual system and exert a profound influence on the brain by adapting it to the language environment. By offering sufficient input, the linguistic competence of the child can grow steadily. Language acquisition is generally completed at the age of 5 or 6 (Vandormael et al., 2019).

Preterm children often reside quite some time in het Neonatal Intensive Care Unit (NICU). This limits the exposure to a linguistically rich environment, because of a lack of parental presence and stimulating speech input. Hence, prematurity often disrupts the language acquisition process, but the extent of this disruption varies widely across preterm children (Vandormael et al., 2019). Furthermore, prematurity can influence all language subdomains. As a consequence, VPT children follow different language trajectories than full-term (FT) children. A study that examined the language trajectories of VPT and FT children from 2 to 13 years in Australia, could differentiate five trajectories. The VPT children had a highly increased likelihood to follow an unstable and/or delayed language trajectory with serious deficits in language acquisition (40% of VPTs displayed this kind of trajectory vs. 6% of the FTs). These language problems were probably already present from infancy. Therefore, they concluded that VPT children should be kept under observation from a young age to stimulate efficient and accurate language acquisition (Nguyen et al., 2018[a]). Very preterm children were also found to have smaller expressive lexicons than FT children at 36 months of age (Brósch-Fohrareim et al., 2019), to be worse at grammar and to demonstrate less phonological awareness at early school-age (Zimmerman, 2018). To illustrate, in the study of Kunnari et al. (2012), Finnish VPT 2-year-olds showed significantly less grammatical growth and made shorter sentences than FT Finnish children.

Two meta-analyses on language outcome in preterm children investigated their simple and complex language functions (Van Noort-van der Spek et al., 2012; Vohr, 2014). Simple language is characterized by the acquisition of separate words and short sentences, whereas complex language involves the integration of multiple components in longer phrases. These two meta-analyses demonstrated that preterm children already perform poorly on simple language tests at a young age. This negative trend continued when examining complex language: with increasing age, preterm children encountered significantly more difficulties with both expressive and receptive language (Van Noort-van der Spek et al., 2012; Vohr, 2014). Because complexity of language increases rapidly during childhood (Stipdonk et al., 2020), this is especially alarming. Both types of language deficits may be the result of a complex interplay of neurobiological and environmental factors (Coughlan et al., 2023; Howard et al., 2011; Vandormael et al., 2019).

1.2 Brain Characteristics of Very Preterm Children

The abnormal language development in VPT children can likely be attributed to the altered and/or damaged brain of these children and its atypical development (Stipdonk et al., 2018). After all, prematurity has a big effect on the structural and functional organization of the brains of preterm children (Vandormael et al., 2019; Vohr et al., 2014). The last trimester of pregnancy is deemed especially crucial for brain maturation, since the human brain undergoes a period of rapid growth because of various cellular processes (e.g., neuronal migration, synaptogenesis and myelination). It includes cortical folding, the development of white matter tracts and a high production of neurons and glial cells (Govaert et al., 2020; Lammertink et al., 2021; Scott et al., 2011). Due to premature exposure to the extrauterine environment, the brains of preterm children are not able to develop completely (Vohr, 2014). This is reflected by commonly found structural brain abnormalities and functional connectivity abnormalities in VPT children.

1.2.1 Structural Brain Alterations

Many magnetic resonance imaging (MRI) studies have revealed significant structural abnormalities in the brains of VPT children compared to FT children, which are already visible on scans at term-equivalent age (TEA). Prominent macrostructural abnormalities include a reduction in total brain volume and decrease in volume of major tissue types (gray matter; white matter) and important brain structures, like the hippocampus and cerebellum (De Kieviet et al., 2012; Story et al., 2021). Moreover, decreased cortical surface area (Gorham et al., 2024; Kelly et al., 2023), increased curvature (Kline et al., 2019, 2020; Makropoulos et al., 2016), and altered cortical folding (Engelhardt et al., 2015) and cortical thickness (Choi et al., 2024; Kelly et al., 2023) patterns were found for VPT children as well. The VPT brain is subject to various long-lasting macrostructural changes in cortical morphometry that may have a cascadic effect on each other and persist into childhood and adulthood. However, for some morphometric parameters, compensatory mechanisms have been observed. A few VPT children demonstrated decreased curvature, and increases in regional brain volumes were identified as well (Karolis et al., 2017; Kim et al., 2022). This implies that the young neuroplastic brains of VPT individuals do show some resilience, and they are (partially) able to recover from perinatal injuries within this respect. The adverse effects of an initially damaged brain may be reversed.

Also on a deeper level, the brain of VPT children exhibits various microstructural alterations. The white matter integrity is often affected by the premature birth. The white matter pathways of VPT infants have fewer axons per fiber bundle (i.e., voxel) and have thinner fiber bundles (restricted space for the axons) (Pannek et al., 2018). Multiple white matter microstructural abnormalities have been reported for VPT children (Dibble et al., 2021). These abnormalities were still visible in important white matter tracts in adulthood. This indicates that VPT born children might not experience catch-up gains regarding large white matter pathways (Kelly et al., 2023). These findings highlight the long-lasting impact of prematurity on brain development and suggest that early interventions may be crucial to mitigate the associated deficits.

1.2.1.1 Language Areas

Upon closer examination of the cortical architecture in VPT children, it becomes apparent that language-related brain areas in VPT children experience different growth trajectories than in FT children. Kvanta et al. (2024) investigated the brain morphometry of relevant language-related regions in EPT children, including the ‘famous’ language regions called Broca’s area and Wernicke’s area. The T1-weighted MRIs were performed at 10 years and language assessment took place at 12 years. The EPT children all had reduced cerebral volumes for almost all language areas, including the inferior frontal gyrus, superior/middle/inferior temporal gyrus, angular gyrus, supramarginal gyrus and supplementary motor area. The inferior frontal gyrus, inferior parietal gyrus and superior/middle/inferior temporal gyrus also demonstrated significant cortical thinning. Several other studies demonstrated similar cortical growth patterns of these language-related regions concerning cortical thickness (e.g., Barnes-Davis et al. [2020]) and brain volume (e.g., Kesler et al. [2008], Soria-Pastor et al. [2009]), especially for male individuals. This implies that the language-related regions in the brains of VPT children might be especially vulnerable, as they are still at the start of development during the last trimester of gestation (Kelly et al., 2024).

1.2.2 Functional Connectivity Abnormalities

The functional organization of the brain in VPT children is often labeled as suboptimal. Resting-state functional magnetic resonance imaging (rsfMRI) is a powerful method to delineate alterations in brain networks that consist of interconnected regions. It aids the identification of brain areas that depend on each other and are part of a larger functional network. Such a network is called a resting-state network (RSN), and can subserve various cognitive processes (Cho et al., 2022; Wehrle et al., 2022).

The networks in VPT infants demonstrated weaker connectivity strength for multiple RSNs, especially for networks underlying higher-order functions. This loss of connectivity is still found in adulthood (Rogers et al., 2018; Wehrle et al., 2022). However, there are also some studies that have discovered increased connectivity between brain areas in certain networks and between networks themselves (e.g., Cho et al., 2022; Wehrle et al., 2022). The language processing network appears to be particularly vulnerable after a premature birth. Gozdas et al. (2018) detected decreased connectivity in neural substrates of expressive language for VPT infants compared to FT infants. In addition, increased connectivity and global efficiency were found in brain regions responsible for auditory processing. According to the authors, these results may indicate that the receptive language skills in preterm infants absorb all their attentional resources and therefore they do not have sufficient cognitive capacity for other language demands, which could lead to a language delay.

1.2.2.1 Language Lateralization

Language lateralization entails the interhemispheric division of language capabilities. In FT humans without cognitive problems, language is mostly lateralized to the left hemisphere. The neural network for language encompasses various frontal and temporal regions in the left hemisphere (Kwon et al., 2015). The study of Kwon et al. (2015) revealed significant differences regarding language lateralization for the left hemisphere between VPT and FT infants at TEA. This was especially pronounced for the frontal and temporal lobe, brain regions of vital importance for expressive and receptive language. The VPT infants had less lateralization and more bilateral activation than the term-born infants. Moreover, the cross-hemispheric connections between two homologous regions were weaker for VPT infants than FT ones. A related study on lateralization of language function in young adults who were born prematurely also revealed increased activation in the right hemisphere and decreased connectivity in the left cerebellum (Rushe et al., 2004).

1.3 Current Study: Neuroimaging Biomarkers of Language Development in Extremely and Very Preterm Children

Survival rates of VPT children have improved in the last few years (Barfield, 2018). As a consequence, the incidence of neurodevelopmental morbidities has increased as well (Jois, 2019). An early start of interventions could minimize the burden of these long-term deficits and improve quality of life. Language is a vulnerable domain often affected by prematurity (Van Noort-van der Spek et al., 2012) and longitudinal studies are necessary to detect which factors contribute to an optimal language development (Vohr, 2014). Neuroplasticity is at its peak in the first years of life and to ameliorate lifelong deficits, an early start of personalized interventions is necessary (He et al., 2021). There probably exist a critical period for language acquisition, indicating that the brain is modifiable, but only until a certain age (Martin et al., 2022). During this period, language problems should be addressed, as otherwise the preterm child will probably never catch-up and exhibit a lifelong developmental delay (Nguyen et al., 2018[a]; Zimmerman, 2018). Therefore, the timely start of effective treatments should be made a top priority for EPT and VPT children.

It would thus be beneficial to know as early as possible which EPT or VPT children might be at risk for language impairment at a later age and which EPT or VPT children may thrive, so that resources will not be wasted and sufficient attention can be paid to the language trajectories of the children at risk. Sanchez et al. (2019) explicitly call for studies that investigate early predictors of language deficits in these populations. This poses quite a challenge, because the rate of lexical and grammatical acquisition varies considerably across preterm children (Kunnari et al., 2012; Stipdonk et al., 2020; Vandormael et al., 2019). Despite a large body of literature on the language development of preterm children (e.g., Barre et al., 2011; Van Noort-van der Spek et al., 2012), the brain is seldom considered in this context. However, the brain holds promising prognostic value for the identification of preterm children that may encounter language difficulties later in life, as language outcomes can often be related to brain structures (Stipdonk et al., 2018). This review bridges the gap between neuroimaging studies on EPT or VPT children and studies focusing on the language development of these children, by discussing the early neuroimaging biomarkers of (impaired) language development in the form of a scoping literature review. The central research question is as follows: *"Which early neuroimaging biomarkers are associated with the (impaired) language development of extremely and very preterm children?"*

The aim of this review is to give an overview of the current knowledge in the field by synthesizing studies that consider both neuroimaging and language development in children born extremely or very premature. Thereby, it hopes to unveil the neural correlates that might be responsible for (impaired) language development and are associated with various language outcomes. In 2018, a literature review on a similar topic was published: Stipdonk et al. (2018). However, this review looked at studies that performed MRI at school-age (6 until 17 years). It would be more valuable to identify early biomarkers at TEA, so that targeted interventions start as early as possible and the detrimental impact of prematurity on language can be attenuated. A language deficit at a later age might already be present in the brain before the onset of language. In addition, the review of Stipdonk et al. (2018) considered all preterm children (born before 37 weeks of gestation), and the authors indicated that their results were inconsistent because of their heterogeneous population (Kvanta et al., 2024; Stipdonk et al., 2018). Therefore, this literature review focuses on EPT and VPT children (≤32 weeks GA), since these children experience even greater language difficulties than moderate-to-late preterm children born between 32 and 36 weeks of gestation (Putnick et al., 2017). Studies were separated in two groups based on the population they investigated: EPT or VPT children. A recent study has pointed out that the incidences of brain injuries differ between EPT and VPT infants (Drommelschmidt et al., 2024). The brain undergoes rapid development in the third trimester, and the early termination of a pregnancy within this critical window can result in different kinds of brain damage (Kvanta et al., 2024).

2. Methods

2.1 Selection of Studies

The computerized database PubMed was searched for articles that looked for neuroimaging biomarkers that could predict the language trajectory of EPT or VPT children. An advanced PubMed search was conducted by only searching in titles or abstracts. The search string was composed of three concepts of interest: population, predictor and outcomes, based on the PICO framework to facilitate literature reviews (Schardt et al., 2007). A broad spectrum of keywords was used, in order to find all relevant articles on the topic of this review. After all, both the brain and language are complex systems composed of multiple components. Whereas language impairment is primarily linked with (impaired) oral language skills, studies investigating the written language skills (such as spelling and reading) of preterm children were included as well to provide a completer picture of the overall language development of these children. Spelling and reading are deemed essential components of language development, but most studies only focus on the oral language ability of preterm children (e.g., see the meta-analyses of Barre et al. [2011] or Van Noort-van der Spek et al. [2012]). Prematurity can have long-term effects on both reading and spelling: several studies pointed out that preterm children had significantly lower scores for reading and spelling than their FT peers (Guarini et al., 2019; Kovachy et al., 2015). Furthermore, language subdomains appear to be interrelated. Optimal phonological awareness is a prerequisite for learning to read (Milankov et al., 2021), and oral language (production and comprehension) can predict reading accuracy (Bonifacci et al., 2024) and spelling abilities (Rvachew et al., 2017). **Figure 1** comprises all the search terms that were combined in the final search string. **Table 1** shows how the three concepts of interest were incorporated in the final search string.

(("extreme* preterm" OR "extreme* prematur*" OR "extremely preterm birth" OR “<28 GA” OR “gestational age < 28” OR “very preterm” OR “very prematur*” OR “very preterm birth” OR “<32 GA” OR “gestational age < 32”) AND (child* OR infant*) NOT (animal* OR mice OR mouse)) AND (brain OR neurological OR neuroimaging OR MRI OR fMRI OR EEG OR ultrasound OR "matter abnormalit*" OR biomarker* OR marker* OR volum* OR cortex OR cortical) AND (language OR linguistic* OR communicat* OR comprehension OR narrative skill* OR narrative ability* OR lexic* OR vocabulary OR semantic* OR phonolog* OR phonem* OR gramma* OR literacy OR literate OR illiteracy OR illiterate OR dyslex* OR synta* OR morphosynta* OR speech OR verbal* OR reading OR spelling OR writing)

Figure 1. *Final search string used in this literature review*

Concepts of Interest	Search Terms
Population: extremely or very preterm infants (≤32 weeks GA)	("extreme* preterm" OR "extreme* prematur*" OR "extremely preterm birth" OR “<28 GA” OR “gestational age < 28” OR “very preterm” OR “very prematur*” OR “very preterm birth” OR “<32 GA” OR “gestational age < 32”) AND (child* OR infant*) NOT (animal* OR mice OR mouse)
Predictor(s): early neuroimaging biomarkers	brain OR neurological OR neuroimaging OR MRI OR fMRI OR EEG OR ultrasound OR "matter abnormalit*" OR biomarker* OR marker* OR volum* OR cortex OR cortical
Outcome: (impaired) language development	language OR linguistic* OR communicat* OR comprehension OR narrative skill* OR narrative ability* OR lexic* OR

	vocabulary OR semantic* OR phonolog* OR phonem* OR gramma* OR literacy OR literate OR illiteracy OR illiterate OR dyslex* OR synta* OR morphosynta* OR speech OR verbal* OR reading OR spelling OR writing

Table 1. *Search terms of advanced PubMed search divided in three concepts of interest*

The study selection process is presented in **Figure 2**. The advanced PubMed search yielded 255 articles. The following inclusion criteria were maintained: (1) the study had a population consisting of an exclusive cohort of EPT or VPT infants (≤32 weeks GA) without major comorbidities[1], (2) the study was considered a longitudinal neuroimaging research (at least >1 year between neuroimaging and language assessment), (3) the neuroimaging took place in the first weeks of life (after birth or at TEA) (4) at least one language outcome was reported, (5) a correlational measure between the neuroimaging biomarker and language outcome was presented, and (6) the study was published in an English peer-reviewed journal. Studies were suitable for inclusion if they met all inclusion criteria. After screening the titles and abstracts, 210 studies were excluded and 45 studies were left. These 45 studies were all assessed for eligibility by full-text reading. Inaccessible studies, study protocols, studies with mixing cohorts (e.g., both VPT children and moderate-to-late premature children)[2], studies consisting of infants with severe brain injuries, congenital malformations and/or neurodegenerative diseases[3] and not controlling for this in the final statistical analyses, studies that considered brain growth at time points after TEA and studies only examining verbal memory were all excluded. There was no requirement for the publication date of the study or for the language assessment tool that was used (i.e., standardized tests). When multiple studies analyzed the same cohort and reported similar brain predictors and comparable kinds of neurodevelopmental outcomes,

[1] According to the World Health Organization (2023), VPT children are born before 32 weeks and most studies follow this classification. However, some studies set the boundary at <33 weeks of GA and still included children born at 32 weeks in their cohort, while defining the cohort as exclusively consisting of VPT children (see Vassar et al. [2020], Montagna et al. [2020] or Kroll et al. [2017]). There is great variability between studies, and it is thus not so clear-cut.

[2] Studies that either used a low birth weight (of certain grams) or a GA at/before 32 weeks as an inclusion criterion were also included, only if the birth weight needed to be 1500 grams or lower. A fetus of 32 weeks GA usually weighs around 1700 grams (Cole et al., 2014; Mayo Clinic, 2022). To ensure all children were born at or before 32 weeks of gestation (and not later), the limit was set at 1500 grams. After all, a very premature birth goes together with a (very) low birth weight.

[3] In previous studies, it was found that major disabilities, biomedical complications or severe brain injuries had a significant influence on the language development of VPT children (Luu et al., 2009; Van Noort-van der Spek et al., 2012; Varela-Moraga et al., 2023). However, studies which included VPT children with intraventricular hemorrhage (IVH) were not excluded from this literature review, since the incidence of IVH among VPT infants is high. Inclusion of these infants ensures the sample of these studies is representative of this population and it results in a larger sample size (Gilard et al., 2020).

only the most recent publication was included. This resulted in 28 studies being included. The characteristics of all included studies is presented in **Table 2**.

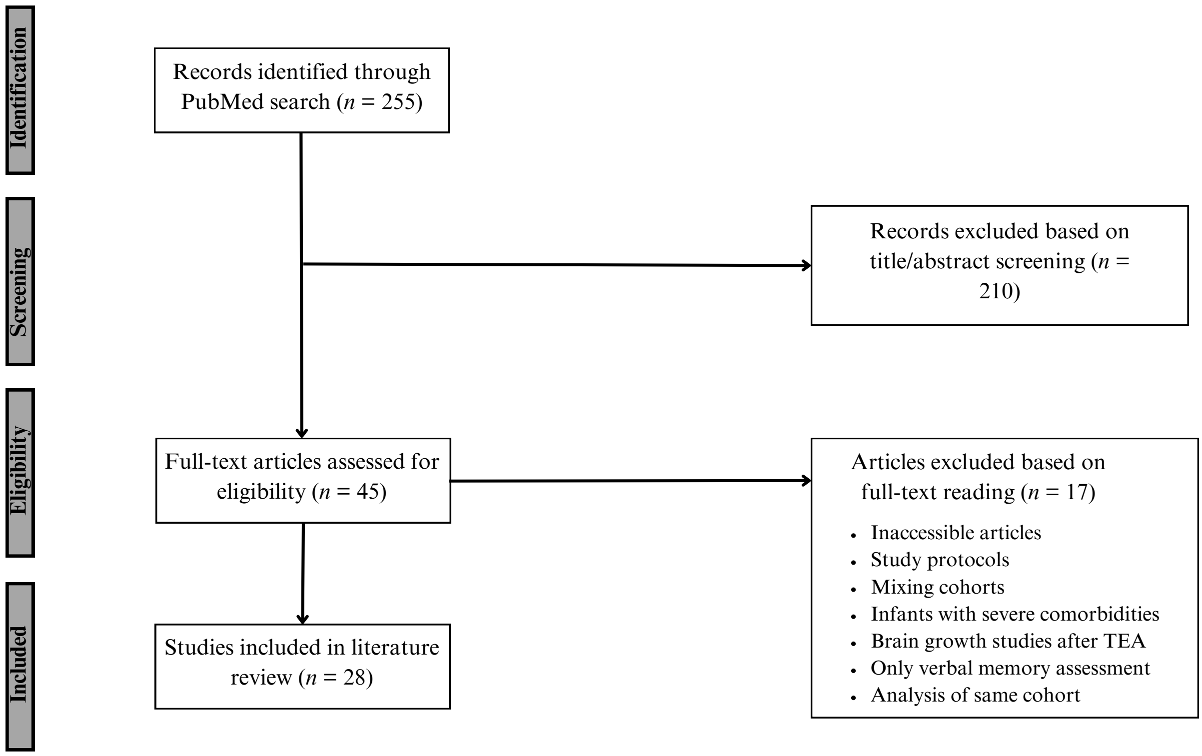

Figure 2. *Flowchart for study selection process*

ID	First Author (year)	Country	Population, n	Neuroimaging Method	Age at Neuroimaging	Predictor(s)	Instrument Language Outcome (subdomain)	Age at Language Outcome	Results
1	Barnes-Davis (2024)	USA	EPT (<28W GA), n = 53	Diffusion MRI (3T)	TEA (39 – 44W PMA)	WM connectivity	BSID- III (expressive & receptive language)	22–26 M*	Bilateral cerebellar WM: - Middle cerebellar peduncles: - Bilateral corticospinal & corticostriatal tracts: - Posterior inferior fronto-occipital fasciculus: - Posterior commissure: -
2	Reis (2024)	USA	VPT (<29W GA), n = 268	Cranial Ultrasound	Before TEA (PMA: 34.5 ±2.8W) or at TEA (PMA: 39.1 ±1.7W)	VBI	BSID- III (expressive & receptive language)	18 – 41 M*	VBI at foramen of Monro: - [β = -9.3, p = .002] Excl. IVH: β = -13.8, p < .001 PMA 34.5: β = -10.6, p = .02 PMA 39.1: β = -7.4, p = .04
3	Schmidbauer (2024)	Austria	EPT (<28W GA), n = 33	(Diffusion) MRI (1.5T)	TEA (PMA: 37^2 $\pm1^3$W)	Relaxometry metrics; WM microstructure	BSID- III (expressive & receptive language)	12 M*	Medulla oblongata: 0 L/R PLIC: 0 Midbrain: 0 Pontine tegmentum:0
4	Trimarco (2024)	Spain	VPT (≤32W GA), n = 116	MRI (1.5T)	Before TEA (PMA: 32.3 ±2.6W) and/or at TEA (PMA: 42.1 ±3.3W)	Brain volumes	BSID- III (expressive & receptive language)	2 Y*	Thalamus: + [β = 9.05, p = .002]
5	Pagnozzi (2023)	Australia	VPT (<31W GA), n = 181	MRI (3T)	Before TEA (29 – 35W PMA)	Brain morphometry: CSF CT GI SA SD Volumes	BSID- III (expressive & receptive language)	2 Y*	CSF volume: - [b = -0.00036] Frontal lobe CT: + [b = 1.96] Frontal lobe SA: - [b = -0.015] Frontal lobe SD: + [b = 0.33] Occipital lobe SD: + [b = 0.24] GI: 0

6	Wang (2023)	Netherlands	EPT (<28W GA), *n* = 369	(a)EEG	Before TEA (first 3 postnatal days)	Machine learning-based regression and classification	WPSSI-III (expressive & receptive language)	5 – 7 Y	Regression: $r = .23$, $p = .003$ Classification: $BA = .81$ [CI 0.65 – 0.96], $p = .001$; $F\beta = .69$ [CI 0.37 – 0.98], $p = .001$
7	Garbi (2022)	France	EPT (<28W GA), *n* = 114	MRI (1.5T)	TEA (39 – 42W PMA)	Standardized scoring systems: 6-point CWM scale 3-point CGM scale CB scale VD DBP IHD TCD	WISC-IV (expressive & receptive language)	7 – 10 Y	CGM lesion – language delay: + [$OR = 3.25$ [CI 1.03 – 9.80], $p = .04$] All other scoring systems: 0
8	He (2021)[a]	USA	VPT (≤32W GA), *n* = 329	(Diffusion) MRI (3T); rsfMRI	TEA (38 – 44W PMA)	Structural connectome Functional connectome DWMA volume	BSID- III (expressive & receptive language)	2 Y*	Structural connectome: + [$r = 0.48 \pm 0.05$; $BA = 76.2$; $AUC = .75$] Functional connectome: + [$r = 0.44 \pm 0.06$; $BA = 74.8$; $AUC = .76$] DWMA: + [$r = 0.39 \pm 0.06$; $BA = 78.4$; $AUC = .78$]
9	Lee (2021)	South-Korea	VPT (<32W GA), *n* = 88 FT, *n* = 38	Diffusion MRI (3T)	NTA (35 – 42W PMA)	WM microstructure of whole-brain WM tracts	BSID- III (expressive & receptive language)	18 – 22 M*	AD values left cingulum pathway: + [$r = 0.22$, $p = .043$] EL: + [$r = 0.23$, $p = .036$]
10	Parikh (2021)	USA	VPT (<32W GA), *n* = 69	Diffusion MRI (3T)	TEA (39 – 44W PMA)	WM microstructure	DAS-II (expressive & receptive language)	3 Y*	0
11	Dubner (2020)	USA	VPT (≤32W GA or birth weight ≤1500 grams), *n* = 30	Diffusion MRI (3T)	TEA (34 – 40W PMA)	WM microstructure	BSID- III (expressive & receptive language)	18 – 24 M*	FA L inferior longitudinal fasciculus: + [$b = 0.58$, $p = .03$] FA corpus callosum occipital segment: - [$b = -0.45$, $p = .02$] Moderated by medical risk: - [$b = -3.56$, $p = .04$] Only negative association for infants with more than 1 medical condition

12	Jansen (2020)	Netherlands	VPT (<32W GA), *n* = 87	MRI (?)	TEA (?)	Standardized scoring systems: Cerebral WM CB abnormality	Dutch Pupil Monitoring System (reading comprehension; spelling)	9 Y	Cerebral WM: 0 CB: 0
13	Kline (2020)[b]	USA	VPT (≤31W GA), *n* = 75	MRI (3T)	TEA (PMA: 40.4 ±0.6W)	Brain morphometry: CT GI ICC SA SD	BSID- III (expressive & receptive language)	22 – 36 M*	SA – L parietal lobe: + [$b = 0.38$, $p = .021$] ICC – L insula: - [$b = -15.02$, $p < .001$] ICC – L superior temporal gyrus: - [$b = -8.59$, $p = .001$]
14	Parikh (2020)	USA	VPT (≤31W GA), *n* = 74	MRI (3T)	TEA (39 – 44W PMA)	DWMA: qualitative quantitative	BSID- III (expressive & receptive language)	2 Y*	Qualitative DWMA: 0 Quantitative DWMA: - [$b = -8.04$, $p = .044$]
15	Vassar (2020)	USA	VPT (≤32W GA), *n* = 92	(Diffusion) MRI (3T)	NTA (?)	WM microstructure; Standardized scoring systems: WM abnormality CB abnormality	BSID- III (expressive & receptive language)	18 – 22 M*	WM microstructure: CL: SENS = 89%; SPEC = 86% > MD R sagittal stratum > AD R lingual gyrus > MD R inferior occipital gyrus EL: SENS = 100%; SPEC = 90% > FA L superior frontal gyrus > AD R sagittal stratum > MD R inferior temporal gyrus RL: SENS = 100%; SPEC = 90% > MD L superior frontal gyrus > AD R superior parietal gyrus > AD R PLIC WM abnormality: 0 CB asymmetry – RL: - [$p = .016$]
16	Matthews (2018)	Australia	VPT (<30W GA or birth weight <1250 grams), *n* = 201 FT, *n* = 41	MRI (1.5T)	TEA (37 – 43W PMA)	Brain volumes	CELF-IV (expressive & receptive language)	7 Y*	Cerebellum: + [$b = 1.01$, $p = .023$] EL: 0 RL: + [$b = 1.01$, $p = .009$]

17	Anderson (2017)	Australia	VPT (<30W GA or birth weight <1250 grams), n = 182	MRI (1.5T)	TEA (38 – 42W PMA)	Standardized scoring systems: GB CGM DGM CWM CB	WRAT-IV (reading & spelling)	7 Y*	Reading: GB: 0 CGM: 0 DGM: - [$b = -3.6$, $p = .045$] CWM: 0 CB: 0 Spelling: GB: - [$b = -1.1$, $p = .029$] CGM: 0 DGM: - [$b = -5.2$, $p = .003$] CWM: 0 CB: 0
18	Keunen (2017)	Netherlands	VPT (<31W GA), n = 30	Diffusion MRI (3T)	TEA (PMA: 41.3 [40.0 – 42.6])	WM microstructure & connectivity	WPSSI-III (expressive & receptive language)	5 Y & 7 M	0
19	Peyton (2017)	USA	VPT (≤31W GA), n = 43	Diffusion MRI (3T)	TEA (34.5 – 42.5W PMA)	WM microstructure	BSID- III (expressive & receptive language)	18 – 24 M*	0
20	Kersbergen (2016)	Netherlands	EPT (≤28W GA), n = 35	MRI (3T)	Before TEA (28.7 – 32.7W PMA) and at TEA (40.0 – 42.7W PMA)	Brain morphometry: Sulcal SA SD Sulcal index	BSID- III (expressive & receptive language)	24 – 30 M*	Before TEA: EL: Sulcal SA L IFS: - [$E = -0.02$, $p = .006$] RL: Sulcal SA L IFS: - [$E = -0.02$, $p = .005$] Sulcal index L IFS: - [$E = -2.1$, $p = .005$] TEA: EL: SD L lateral fissure: + [$E = 0.13$, $p = .006$] RL:[b] Hemisphere size bilateral: + [$E = 0.21$, $p = .001$] Sulcal SA L lateral fissure: + [$E = 0.11$, $p = .002$] SD L lateral fissure: + [$E = 0.14$, $p = .0005$] Sulcal index L lateral fissure: + [$E = 0.12$, $p = .002$]
21	Monson (2016)	Australia	VPT (<30W GA or birth weight	MRI (1.5T)	TEA (38 – 42W PMA)	Brain volumes	CELF-IV (expressive & receptive	7 Y*	CGM: RL: + [$r = 0.29$, $p < .05$] Semantics: + [$r = 0.29$, $p < .05$] DGM:

			<1250 grams), n = 198 FT, n = 43				language; grammar; semantics)		RL: + [r = 0.29, p < .05] WM: + [r = 0.29, p < .05] RL: + [r = 0.32, p < .05] Grammar: + [r = 0.31, p < .05] Semantics: + [r = 0.30, p < .05]
22	Young (2015)	Canada	VPT (≤32W GA), n = 45	MRI (1.5T)	Before TEA (25 – 35W PMA) and TEA (36 – 46W PMA)	Brain volumes	CELF-Pre-II (expressive & receptive language; grammar; semantics)	4 Y	Caudate (growth): 0 GB (growth): 0 Putamen growth: + [F-change = 5.224, p = .028] Thalamus (growth): 0
23	Skiöld (2014)	Sweden	EPT (<27W GA), n = 56	(Diffusion) MRI (1.5T)	TEA (PMA: 40[5] ±1W)	Brain volumes; WM microstructure	BSID- III (expressive & receptive language)	30 M*	Brain volumes *Boys:* 0 *Girls*: CGM: + [r = 0.54, p = .03] CGM cingulate: + [r = 0.70, p < .001] EL: WM: + [r = 0.58, p = .02] WM precuneus: + [r = 0.75, p < .01] DGM: + [r = 0.60, p = .01] Brain stem: + [r = 0.51, p = .03] WM microstructure: 0
24	He (2013)	USA	VPT (<31W GA), n = 38	MRI (3T)	TEA (34 – 43W PMA)	DWMA volume	BSID- III (expressive & receptive language)	2 Y	Global WM region: - [r = -0.47, p = .003] Periventricular region: - [r = -0.44, p = .006] Centrum semiovale region: - [r = -0.63, p < .0001]
25	Reidy (2013)	Australia	VPT (<30W GA or birth weight <1250 grams), n = 193 FT, n = 70	MRI (1.5T)	TEA (?)	Standardized scoring system: WM abnormality	NEPSY-II (phonological awareness) and CELF-IV (semantics, pragmatics,	7 Y*	Phonological awareness: - [b = -0.5, p = .001] Semantics: 0 Grammar: 0 Discourse: 0 Pragmatics: 0

							discourse, grammar)		
26	Skiöld (2012)	Sweden	EPT (<27W GA), *n* = 91 FT, *n* = 78	MRI (1.5T)	TEA (38 – 41W PMA)	Standardized scoring system: WM abnormality	BSID- III (expressive & receptive language)	30 M*	Mann-Whitney U test between no-mild WM abnormality vs. moderate-severe WM abnormality: $p < .05$
27	Woodward (2012)	New Zealand	VPT (≤32W GA), *n* = 106/104 FT, *n* = 108	MRI (1.5T)	TEA (39 – 41W PMA)	Standardized scoring system: WM abnormality	CELF-P (expressive & receptive language) > 4Y and WJ-III (receptive language) > 6Y	4 Y* and 6 Y*	WM signal abnormality: - [$r = -0.31$ (4Y); -0.32 (6Y), $p \leq .002$] Reduced WM volume: - [$r = -0.31$ (4Y); -0.36 (6Y), $p \leq .002$] Thinning corpus callosum: - [$r = -0.24$ (4Y); -0.30 (6Y), $p \leq .02$] Cystic abnormality: - [$r = -0.30$ (4Y); -0.38 (6Y), $p \leq .002$] Ventricular dilatation: 0
28	Nosarti (2011)	United Kingdom	VPT (≤32W GA), *n* = 120 FT, *n* = 50	Cranial Ultrasound	Before TEA (first 4 postnatal days)	Cranial ultrasound abnormality classification: Normal PVH PVH + VD	COWAT (phonemic verbal fluency) and ANONT (semantic verbal fluency) and SGRT (reading) and SST (spelling)	14 – 15 Y	Phonological verbal fluency: 0 Semantic verbal fluency: 0 Reading: 0 Spelling: 0

Table 2. *Overview of the main study characteristics per included study: reference (author/year), country, population, neuroimaging method, age at neuroimaging, language outcome instrument, age at language outcome and key results*

Note: AD = axial diffusivity; (a)EEG = (amplitude-integrated) electroencephalography; ANONT = Animal Naming and Object Naming Test; AUC = area under the curve; BA = balanced accuracy; BSID-III = Bayley Scales of Infant and Toddler Development, third edition; CB = cerebellum; CELF(-IV/P/Pre-II) = Clinical Evaluation of Language Fundamentals, fourth edition/preschool/preschool second edition; CGM = cortical gray matter; CI = confidence interval; CL = core language (language composite score); COWAT = Controlled Oral Word Association Test; CSF = cerebrospinal fluid;

CT = cortical thickness; CWM = cortical white matter; DAS-II = Differential Ability Scales, second edition; DGM = deep gray matter; DPB = diameter biparietal; DWMA = diffuse white matter abnormalities; EL = expressive language; EPT = extremely preterm; GA = gestational age; FA = fractional anisotropy; FT = full-term; GB = global brain; GI = gyrification index; ICC = inner cortical curvature; IFS = inferior frontal sulcus; IHD = interhemispheric distance; IVH = intraventricular hemorrhage; L = left; M = months; MD = mean diffusivity; MRI = magnetic resonance imaging; NEPSY-II = developmental neuropsychological assessment, second edition; NTA = near-term age; OR = odds ratio; PLIC = posterior limb of internal capsule; PMA = post-menstrual age; PVH = periventricular hemorrhage; R = right; RL = receptive language; rsfMRI = resting-state fMRI; SA = surface area; SD = sulcal depth; SENS = sensitivity; SGRT = Schonnel Graded Reading Test; SPEC = specificity; SST = Schonnel Spelling Test; TCD = trans-cerebellar distance; TEA = term-equivalent age; VBI = ventricle-to-brain index; VD = ventricular dilatation; VPT = very preterm; W = weeks; WJ-III = Woodcock Johnson Tests of Achievement, third edition; WM = white matter; WPSSI-III = Wechsler Preschool & Primary Scale of Intelligence, third edition; WRAT-IV = Wide Range Academic Test, fourth edition; Y = years

'-' indicates a significant negative correlation; '+' indicates a significant positive correlation; '0' indicates an insignificant correlation

* Age represents corrected age for prematurity

[a] Multiple discriminative region-to-region structural/functional connections have been identified to be predictive of a language deficit, but these were too many to include in this table.

[b] Only the most robust significant predictive findings are included.

2.2 Measures

2.2.1 Neuroimaging

In this scoping review, various neuroimaging modalities will be discussed. **Table 3** provides a comprehensive overview of the neuroimaging modalities used by the included studies in this review. The most prevalent method is (structural) MRI. T1-weighted and T2-weighted MRI sequences are adequate for an in-vivo view of the brain with great anatomical detail, which facilitates the detection of structural abnormalities. Morphological characteristics can also be measured efficiently with structural MRI to study macrostructural changes in cortical thickness, brain volumes and surface area, for instance (Gaser, 2016; Liu, 2016; Symms et al., 2004).

Diffusion-weighted imaging (DWI) is a subcategory of MRI, therefore also often labeled diffusion MRI. It is dependent on the direction and magnitude of water molecules. Consequently, this technique is able to demonstrate white matter integrity (Schaefer et al., 2000). Diffusion tensor imaging (DTI) is the most conventional form of DWI. It can visualize structural connectivity and white matter tracts. Fractional anisotropy (FA) and mean diffusivity (MD) can be measured with DTI. FA is used as an index of directional coherence, the directionality of water molecules within a voxel. It represents a value between 0 (unrestricted diffusion) and 1 (diffusion along one specific axis) (Clark et al., 2020; Labus et al., 2020; Ranzenberger & Snyder, 2022). Mean diffusivity, sometimes labeled apparent diffusion coefficient (ADC), measures the overall diffusion of water molecules within brain tissue. It is calculated by averaging diffusion values along different axes. These values comprise axial diffusivity (AD) and radial diffusivity (RD) (Evans et al., 2023; Salat, 2014).

To visualize the interrelated connectivity and functional organization of brain regions, functional MRI (fMRI) can be used. This neuroimaging technique can potentially reveal which brain areas belong to large-scale neural circuits by working together in accomplishing tasks or are involved in connected neural networks during resting state (Rogers et al., 2007).

Cranial ultrasound or ultrasonography provides an accessible tool for screening preterm and high-risk neonates and evaluating their brains for damage. The ultrasound machine sends sound waves into the infant’s head, and these sound waves get reflected back. This way, an image is created of the global brain and ventricles (Locke & Kanekar, 2022; Roufaeil et al., 2022).

Electroencephalography (EEG) measures the electrical activity of the brain. Various electrodes are placed on the infant’s scalp to record voltage potentials. It has a good temporal resolution and has the potential to determine which infants without overt brain damage are at the greatest risk for long-term neurodevelopmental deficits (Biasiucci et al., 2019; Wang et al., 2023). Amplitude-integrated EEG (aEEG) is a simplified version of conventional multichannel EEG, since its recording is restricted to only two or four scalp electrodes (Bruns et al., 2017; Glass et al., 2013).

Neuroimaging Modality	Outcome Variables	Explanation
Cranial ultrasound	N.A.	Image is created of infant's brain to view possible brain damage
(a)EEG	N.A.	Electrical activity is captured to determine infants at increased risk for long-term adverse effects
Diffusion MRI	Apparent diffusion coefficient Axial diffusivity Fractional anisotropy Mean diffusivity Radial diffusivity	White matter microstructure and connectivity are assessed by measuring the direction and magnitude of water molecules
fMRI	N.A.	Functional organization reveals which brain areas work together in neural networks
Structural MRI	Morphometric parameters Brain volumes Cortical thickness Gyrification index Inner cortical curvature Sulcal depth Surface area Structural abnormalities	Structural abnormalities are clearly visible on T1/T2 MRI scans and various morphometric parameters can be measured which provide information on the shape and size of the brain

Table 3. *Overview of the neuroimaging modalities and their associated outcome variables*
Note: N.A. = not applicable

2.2.2 Language

The 28 included studies used a wide range of language assessment instruments. These language assessment instruments can broadly be divided in four categories: oral language, phonological awareness, verbal fluency and written language. **Table 4** contains an overview of all language instruments that were used to test certain language subdomains, divided over the four main categories.

Oral language abilities concern expressive and receptive language in general. The child's vocabulary is tested by naming pictures, but the child is also tested for the comprehension of sentences. The Bayley Scales of Infant and Toddler Development-III (BSID, third edition) is a norm-referenced instrument to diagnose developmental delays, including language delays. It investigates the oral (expressive and receptive) language skills of young children, usually around 2 years of corrected age (CA) (Balasundaram & Avulakunta, 2022). A similar test is the Differential Ability Scales-II (DAS), which renders a verbal ability score that represents expressive and receptive oral language skills (Parikh et al., 2021). The Clinical Evaluation of Language Fundamentals (CELF) is also often utilized to test these skills, but it delves more deeply into the language abilities of children. It also focuses on grammar and semantics. In addition, caregivers are asked to fill in a document about the communication skills of the child. There is a preschool version, suitable for children aged 3 to 7 years, and a standard version, suitable for individuals aged 7 to 21 years (Pearson Education, n.d.). The subtest understanding directions from the Woodcock-Johnson Tests of Achievement-III (WJ) is another advanced test that taps into the receptive ability of school-aged children (Woodward et al., 2012). Finally, the verbal scales of the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI) and Wechsler Intelligence Scale for Children-III (WISC) were used to assess the expressive and receptive language abilities of children. These are both general IQ tests, but the verbal IQ (WPPSI) or verbal comprehension index (WISC) can give an indication of the language skills of these children. The WPPSI is generally used until the age of 6 or 7, while the WISC is suitable for children between 6 and 16 years (Auris Audiologisch Centrum, n.d.; Pearson Clinical Assessment, n.d.; Wang et al., 2023).

Phonological awareness encompasses the auditory comprehension of speech sounds and the oral manipulation of them (Milankov et al., 2021). The subtest phonological processing of the Developmental Neuropsychological Assessment (NEPSY-II) tests this ability (Harcourt Assessment, 2007; Visu-Petra et al., 2012).

Verbal fluency involves the ability to generate specific words. Besides, it assesses executive functions, such as mental flexibility and onset of response. Verbal fluency can be divided in phonemic and semantic fluency. The Controlled Oral Word Association Test (COWAT) measures phonemic fluency. Individuals are then asked to produce as many words as possible starting with a specific letter. In the Animal Naming and Object Naming Test (ANONT) participants are asked to name as many words as possible from a specific category (Nosarti et al., 2011).

Producing and understanding written language is assessed only in older children (from approximately 7 years), as this is a complex skill that takes time to master. Reading is a receptive skill that can be measured with the Schonnel Graded Reading Test (SGRT). The complementary Schonnel Spelling Test (SST) measures the spelling skills of children, but these tests are both quite old (Nosarti et al., 2011). The Wide Range Achievement Test-IV (WRAT) is a more recent test that also estimates those two academic skills (Anderson et al., 2017). Furthermore, standardized school grading systems of academic achievement are useful candidates to assess the reading and spelling abilities of children.

Language Category	Language Subdomain	Language Instrument(s)
Phonological awareness	N.A.	NEPSY-II
Oral language	Expressive language	BSID-III; CELF; DAS-II; WISC-III; WPPSI-III
	Grammar	CELF
	Pragmatics	CELF
	Receptive language	BSID-III; CELF; DAS-II; WISC-III; WPPSI-III; WJ-III

	Semantics	CELF
Verbal fluency	Phonemic fluency	COWAT
	Semantic fluency	ANONT
Written language	Reading	SGRT; WRAT-IV; standardized school grading systems
	Writing	SST; WRAT-IV; standardized school grading systems

Table 4. *Overview of the four language categories, their associated language subdomains and the language instruments used to test these subdomains*

Note: ANONT = Animal Naming and Object Naming Test; BSID-III = Bayley Scales of Infant and Toddler Development, third edition; CELF = Clinical Evaluation of Language Fundamentals; COWAT = Controlled Oral Word Association Test; DAS-II = Differential Ability Scales, second edition; N.A. = not applicable; NEPSY-II = Developmental Neuropsychological Assessment, second edition; SGRT = Schonnel Graded Reading Test; SST = Schonnel Spelling Test; WJ-III = Woodcock Johnson Tests of Achievement, third edition; WPPSI-III = Wechsler Preschool and Primary Scale of Intelligence, third edition; WRAT-IV = Wide Range Achievement Test, fourth edition

2.2 Correlational Measures

The reported correlational measure between the neuroimaging predictor and language outcome was extracted from each study and presented in the utmost right column of **Table 2**. The included studies used different kinds of research designs. Most studies used an univariable or multivariable linear regression model to calculate if there were any significant associations between the neuroimaging predictor and language outcome. Other studies reported Pearson's correlational coefficient or used a logistic regression model. In addition, higher-order diffusion models and innovative techniques were used to measure correlations, like deterministic tractography and correlational connectometry. Some studies even employed machine learning techniques and set up classification models to discover potential predictors of language development. Finally, two studies that graded brain abnormalities on standardized scales performed a Mann-Whitney U test or conducted an ANCOVA analysis between the different categories of abnormalities [**26; 28**].[4]

When multiple correlational measures were reported, the measures that were included in a multivariable model with covariates (related to brain injuries or medical conditions) were chosen. The studies that used standardized abnormality scales as predictors all followed a similar principle: the higher the score, the more brain abnormalities were identified. To illustrate, a negative correlation between such a predictor and language outcome indicates that a lower language score goes together with more brain injury.

[4] These numbers between brackets represent the study IDs in the first column from **Table 2**.

3. Results

In total, 28 studies were included (details of individual studies are stated in **Table 2**). Ten of these studies were conducted in the United States, five in Australia, four in The Netherlands, two in Sweden, and the remaining nine in various other countries. All 28 studies used a wide variety of neuroimaging methods, some of them even combining methods into one research design. Structural MRI was the most popular method, as it was applied in 18 studies. Diffusion MRI was employed by ten studies, cranial ultrasound by two, and EEG and fMRI were used only once. All neuroimaging methods were used around TEA. The age of the infants at the application of these neuroimaging techniques ranged from the first three postnatal days [**6**] to 46 weeks post-menstrual age (PMA) [**22**].

Furthermore, a broad spectrum of neuroimaging biomarkers was explored by the included 28 studies. White matter microstructure and connectivity as a potential predictor was investigated by ten separate studies. Nine studies used standardized scales to assess the predictive power of brain or ventricular abnormalities. In addition, the prognostic value of brain volumes was the focus of eight studies. Three studies further investigated the overall relationship between brain morphometry (e.g., cortical thickness, surface area and sulcal depth, etc.) and language outcomes to provide a more complete picture. The predictive power of EEG, fMRI, relaxometry metrics and a ventricular index was assessed only once.

The BSID-III was the most frequently used language assessment tool (n = 16). The CELF (three different versions) was used by five separate studies, and the WPSSI-III by two Dutch studies. All other standardized language tests or instruments were used only once. Language assessment was performed from 12 months CA [**3**] until adolescence at approximately 15 years [**28**].

3.1 Very Preterm Children

In total, 21 studies investigated the potential of various neuroimaging biomarkers to predict language outcomes in VPT children (≤32 weeks GA [**2**; **4-5**; **8-19**; **21-22**; **24-25**; **27-28**]). These studies also included EPT children. Studies that exclusively examined EPT children will be discussed in **paragraph 3.2**. An overview of the main findings of the 21 VPT studies regarding the correlation between early neuroimaging biomarkers and language development can be viewed in **Table A1** in the Appendix.

3.1.1 Brain Morphometry

Pagnozzi et al. [**5**] performed an advanced and extensive study to identify MRI biomarkers using the developing Human Connectome Pipeline. This algorithm processes and segments the MRI data and provides a list of interesting metrics regarding cortical thickness (CT), gyrification index (GI), surface area (SA), sulcal depth (SD) and anatomical volumes. The multivariable regression models showed that cortical thickness and sulcal depth of the frontal lobe were both positively associated with language outcomes, while surface area of that lobe was negatively correlated with language. Sulcal depth of the occipital lobe showed another positive association with language. Gyrification index was not retained in the model due to insignificance. Kline et al. [**13**] also explored the cerebral effects of a very premature birth on neurodevelopmental outcomes. They expanded the rich palette of morphometric parameters (CT; GI; SA; SD) with an extra parameter: inner cortical curvature (curvature of white matter). A multivariable regression model included the following significant metrics: surface area of the left parietal lobe (positive correlation) and curvature of the left insula and superior temporal gyrus (negative correlations). The other parameters (CT; GI; SD) were significant in bivariable models, but covariates canceled out their effects.

3.1.1.1 Brain Volumes

Trimarco et al. [**4**] concentrated in their study on the growth trajectory of the thalamus. They performed volumetric analyses before and at TEA by scanning VPT infants twice in an MRI scanner. The growth of the thalamus in this chronological time period showed a significant positive correlation with language development around 2 years CA, after correction for several covariates. The growth of the thalamus (during the third trimester) was again investigated by Young et al. [**22**], along with the caudate nucleus, globus pallidus, putamen and the total brain. They used hierarchical regression to identify the predictive power of the volumetric growth and cross-sectional (before TEA; TEA) volumes of these brain areas for various neuropsychological outcomes. The cross-sectional volumes and growth of the thalamus were not indicative of language development this time, but the growth of the putamen demonstrated a significant positive correlation with language.

Matthews et al. [**16**] conducted a similar study for the cerebellum. They measured cerebellar volumes at TEA in VPT infants and followed up with another scan at 7 years to analyze the growth trajectory of this region. Cerebellar neonatal volumes were positively associated with language, particularly with receptive language.[5] Monson et al. [**21**] performed a comparable study (also MRI scans both at TEA and 7 years), but for the main cerebral tissue volumes (cortical and deep gray matter; white matter). Strong evidence was found for the influence of early tissue volumes on language development. Expressive language, receptive language, semantics and grammar skills all showed significant positive associations with the volumes of these brain tissues.

The volumes of major tissue types were the topic of multiple studies. Pagnozzi et al. [**5**] found a negative association between cerebrospinal fluid (CSF) and language. This is not surprising, as ventricular dilatation is one of the most identified brain injuries in preterm infants (Sheng et al., 2022).

Some studies enlarged the scope of these volumetric analyses and quantified brain abnormalities by calculating their volumes from structural MRI data. He et al. [**8**] quantified white

[5] Only the TEA volumes were of interest to this literature review (see inclusion criteria in **2. Methods**).

matter abnormalities with an in-house developed algorithm. The volume of white matter abnormalities was a good predictor (accuracy of 78.4%) of the VPT children that were at high risk for future language impairment (next to the structural and functional connectome). In the cohort from 2007 to 2009 [**24**], it had already become apparent that this method was quite effective in identifying children who showed signs of an early language deficit. He and Parikh [**24**] investigated the utility of this method for three regions of interest especially vulnerable to diffuse excessive high signal intensity. The automated quantified white matter abnormalities at the centrum semi-ovale, periventricular crossroads and of the total white matter region all negatively correlated with language scores at 2 years.

In Parikh et al. [**14**] this method was used again. The predictive power of the objectively acquired white matter abnormality volumes was contrasted with the predictive power of qualitatively diagnosed white matter abnormalities using a standardized scale. The white matter abnormality volumes showed a significant negative correlation with language scores, the qualitatively diagnosed white matter abnormalities did not.

3.1.2 White Matter Microstructure and Connectivity

The white matter integrity of different tracts was analyzed by a study in South-Korea [**9**]. Partial correlations were performed to relate white matter microstructure to clinical outcomes. Axial diffusivity was significantly positively correlated with language in the left cingulum pathway, especially for expressive language, but FA showed no correlations at all. A comparable study was conducted by Parikh et al. [**10**], however they assessed the contribution of FA and MD, not AD. Significant results for language development were absent for both FA, just as for Lee et al. [**9**], and MD. Similarly, Dubner et al. [**11**] aimed to research the neurobiological basis of impaired language skills at an early age by calculating FA and MD of five prominent white matter pathways deemed important for the transfer of linguistic information. None of the regression models that included MD were significant, but the FA of the left inferior longitudinal fasciculus was positively associated with language. This was a distinct neural pathway with high structural connectivity, especially for preterm children with high language scores. The FA of the corpus callosum occipital segment was negatively correlated with language, moderated by the number of medical conditions an infant was subjected to.

Vassar et al. [**15**] used near-term DTI imaging and statistical learning to identify three brain regions whose white matter microstructure strongly predicted infants with an increased risk of language impairment at a later age. Evidence was found that the sagittal stratum, posterior limb of the internal capsule (PLIC) and various large gyri all were essential regions for accurate predictions. A different study approached white matter microstructure with whole brain and deterministic streamline tractography [**18**], but this method was less successful in correlating the average FA of all connections between 56 regions of interest with verbal IQ. The prognostic value of white matter microstructure was also examined by Peyton et al. [**19**]. They used tract-based spatial statistics analysis, but drew a similar conclusion: none of the voxels showed a linear relationship between FA and language scores, and the FA values of poor children did not differ from children showing excellent language skills.

A different study explored the overall structural connectome of the young VPT brain as a potential predictor of a language deficit at 2 years CA [**8**]. Using integrative and deep machine learning models, they reached an accuracy of 76.2%, which is quite substantial.

The overall structural connectome of the young VPT brain as a potential predictor of a language deficit at 2 years CA was explored by a study using integrative and deep machine learning models [**8**]. They reached an accuracy of 76.2%, which is quite substantial. Another study was devoted to the structural network organization of white matter and its connectivity strength in the neonatal brain [**18**]. Correlations between language and either connectivity strength, global efficiency or network clustering were not found around 6 years of age.

3.1.3 Structural Abnormalities

A Dutch study was conducted in 2020 to measure to what extent white matter abnormalities and cerebellar abnormalities influence the reading and writing skills of 9-year-old VPT children [**12**]. The researchers assessed these skills using the Dutch Pupil Monitoring System, which monitors the academic progress of these children across school grades. The VPT children in the lowest categories of school performance for reading and spelling did not have different white matter or cerebellar abnormality scores than the children in the highest categories. Parikh et al. [**14**] found that moderate-severe white matter abnormalities that were diagnosed qualitatively could also not predict impaired oral language skills at 2 years CA. Vassar et al. [**15**] confirmed these findings, as they also could not find a significant association between white matter abnormalities, assessed with a neuroradiological classification system, and language outcomes. However, cerebellar abnormality (primarily asymmetry) was negatively associated with receptive language scores.

Anderson et al. [**17**] thoroughly investigated the influence of neonatal MRI abnormalities on written language (reading and spelling) in 7-year-old VPT children. These brain abnormalities were assessed on four separate standardized scales: cerebellum, white matter, cortical and deep gray matter. The scores of all scales together represented the global brain score. Serious structural brain abnormalities in VPT infants were found for all four scales, but only higher abnormality scores for deep gray matter were significantly related to poorer reading ($p = .045$) and spelling ($p = .003$). Furthermore, the global brain score did also significantly correlate with spelling ($p = .029$). Therefore, (the circuit of) all these brain regions or tissues together could function as the neural substrate of a deficit in written spelling at school-age.

Reidy et al. [**25**] used a large number of language tests to measure the impact of white matter abnormalities (scored on a standardized scale) on phonological awareness, semantics, pragmatics/discourse and grammar. Mediation analyses were performed to see if and how white matter abnormalities mediated the relationship between birth group (FT vs. VPT) and language outcomes. The VPT children scored significantly worse on the tests than the FT children: only for phonological awareness this could be attributed to the number and type of white matter abnormalities found in VPT children. Woodward et al. [**27**] also explored the role of structural white matter abnormalities in predicting neurocognitive outcomes, but they delved deeper into the white matter abnormality scale by also grading the five subscales it was composed of. Moreover, they assessed language twice at two separate follow-up moments: 4 and 6 years of CA. Four of the five subscales were significant predictors of language development at both time points: general signal abnormality, reduced volume, cystic abnormalities and thinning of the corpus callosum.

Finally, Nosarti et al. [**28**] classified VPT infants in three categories based on abnormalities that were determined by cranial ultrasound: normal, periventricular hemorrhage, and periventricular hemorrhage with ventricular dilatation. They assessed phonemic and semantic verbal fluency, even as two educational outcomes: reading and spelling. After controlling for multiple relevant factors, no significant associations were found between language outcomes and neonatal cranial ultrasonography.

3.1.4 Miscellaneous Predictors

Reis et al. [**2**] calculated a ventricle-to-brain index (VBI) at the foramen of Monro. Ventricular dilatation of the third ventricle was previously determined to be a reliable predictor of future cognitive and linguistic impairments. They investigated with cranial ultrasound whether this predictor could be extended to the ventricular channel that interconnects the lateral ventricles with the third ventricle. The VBI was a highly significant predictor, since the analyses showed a strong negative correlation between BSID-III language outcomes and the VBI.

He et al. [**8**] made use of resting-state fMRI to display the functional connectivity between various brain areas in 329 VPT infants and to test whether this could predict a language deficit at 2 years CA. The validated model had a high accuracy for identifying children that were at an increased risk for a language deficit.

3.2 Extremely Preterm Children

In total, seven studies had a population consisting of EPT children (<28 weeks GA [**1**; **3**; **6-7**; **20**; **23**; **26**]). The main outcomes of these studies regarding the correlation between early brain markers and language development are summarized in **Table A2** in the Appendix.

3.2.1 Brain Morphometry

Only one study attempted to investigate the brain morphometry of EPT infants in order to find relevant neuroanatomical characteristics that could be associated with neurodevelopmental outcomes at 2 years of age [**20**]. Kersbergen et al. (2016) paid exclusive attention to the development of sulcal characteristics before and at TEA. Cortical folding primarily happens in the last trimester of gestation, and for EPT children this takes place outside the womb. General linear modelling revealed various significant correlations. For expressive language, only two correlations were found. A negative correlation with the sulcal surface area of the left inferior frontal sulcus (IFS) and a positive correlation with the sulcal depth of the left lateral fissure (LF). The left LF demonstrated to be a promising landmark, as its surface area, sulcal depth and sulcal index were also positively related to receptive language. The sulcal surface area and sulcal index of the left IFS again showed a negative association, now with receptive language.

3.2.1.1 Brain Volumes

A study conducted in Sweden analyzed the major tissue type volumes (of certain brain areas). The study investigated to what extent these volumes showed an association with long-term outcomes for EPT boys and girls at 30 months CA [**23**]. They could not detect any significant associations between these volumes and language outcomes for boys. In contrast, cortical gray matter, white matter and brain stem volumes were significantly higher for girls with higher language scores. Extra regional analyses showed these significant associations could probably be attributed to two regions: the cingulate gyrus (cortical gray matter) and precuneus (white matter).

3.2.2 White Matter Microstructure and Connectivity

To study brain maturation in EPT infants, three studies explored the role of white matter microstructure and connectivity strength in predicting language outcomes later in life [**1**; **3**; **23**]. One study [**3**] did not find significant associations between two DTI metrics of five specific brain areas and language outcomes. A study by Skiöld et al. [**23**] investigated similar DTI metrics (ADC and FA) and arrived at the same result: no significant differences were observed in diffusion measures for EPTs with different language scores. On the other hand, Barnes-Davis et al. [**1**] demonstrated with advanced connectometry techniques and higher-order diffusion models that there exist many negative associations between the structural connectivity of white matter tracts and language outcomes. These include the cerebellum (bilateral), middle cerebellar peduncles, corticospinal and corticostriatal tracts (bilateral), the posterior inferior fronto-occipital fasciculus and posterior commissure. The fibers along these pathways have significantly different orientations, probably causing reduced connectivity.

3.2.3 Structural Abnormalities

Garbi et al. [**7**] used seven different standardized scoring systems to identify brain abnormalities on structural MRI scans. They divided their study population into two groups: school-aged children with a language delay (verbal IQ less than 85, one SD of the norm) and those without a delay. The odds ratio of experiencing impaired language development was only significant for the children with moderate to severe cortical gray matter lesions, not for the individuals with white matter or cerebellar abnormalities. Skiöld et al. [**26**] only examined white matter abnormalities but reached a different conclusion. Their Mann-Whitney U test revealed a specific ranking: young EPT children with moderate to severe white matter abnormalities had the lowest BSID-III scores, then EPT children with no or mild abnormalities, while the FT children scored the highest.

3.2.4 Miscellaneous Predictors

The relationship between innovative, quantitative relaxometry MRI metrics (T1 and T2) and language development was analyzed by one study [**3**]. There was no significant relationship between the relaxation times of the PLIC and parts of the brain stem with language development at 12 months CA.

Wang et al. [**6**] examined the predictive power of EEG and aEEG features within the first three postnatal days for neurodevelopmental outcomes at 5 to 7 years of age. Verbal IQ could be accurately predicted by machine learning-based classifiers, and the model showed robust performance in discriminating between infants with a language disorder and infants with an optimal language trajectory.

3.3 Extremely Preterm and Very Preterm Children

Table 5 provides an overview of the significant and insignificant biomarkers per preterm group. It functions as a global summary of **Tables A1** and **A2,** which contain detailed information of individual studies. In **Table 5** the number of significant or insignificant biomarkers is presented for each neuroimaging biomarker category. The studies that show support for this are included between brackets. No large differences in the prognostic value of neuroimaging biomarkers between EPT and VPT children were found. Brain morphometry, brain volumes and miscellaneous predictors had the most predictive power and showed robust correlations with language for both groups. Structural abnormalities and white matter microstructure and connectivity were weak predictors of language development, since most studies could not find any significant associations between these biomarkers and language outcomes.

	Extremely Preterm Children	Very Preterm Children
Brain Morphometry	Significant: 3 [**20**] Insignificant: 0	Significant: 4 [**5**; **13**] Insignificant: 1 [**5**]
Brain Volumes	Significant: 4 [**23**] Insignificant: 0	Significant: 8 [**4**; **5**; **8**; **14**; **16**; **21**; **22**; **24**] Insignificant: 5 [**16**; **22**]
WM Microstructure & Connectivity	Significant: 1 [**1**] Insignificant: 2 [**3**; **23**]	Significant: 4 [**8**; **9**; **11**; **15**] Insignificant: 3 [**9**; **10**; **11**; **18**; **19**]
Structural Abnormalities	Significant: 2 [**7**; **26**] Insignificant: 6 [**7**]	Significant: 4 [**15**; **17**; **25**; **27**] Insignificant: 5 [**12**; **14**; **15**; **17**; **25**; **27**; **28**]
Miscellaneous Predictors	Significant: 1 [**6**] Insignificant: 1 [**3**]	Significant: 2 [**2**; **8**] Insignificant: 0

Table 5. *Summary of the study results indicating the number of significant and insignificant neuroimaging biomarkers per category for EPT and VPT children*

Note: the neuroimaging biomarkers have been divided into separate categories (e.g., brain volumes or white matter microstructure & connectivity). These neuroimaging categories have been divided again in separate biomarkers (e.g., SA or SD for brain morphometry; volumes of different brain regions for brain volumes; MD or FA for white matter microstructure; different standardized abnormality scales for structural abnormalities; T1/T2 RT, EEG, fMRI or VBI for miscellaneous predictors). All these separate biomarkers are included in this table (exact location of the biomarker was not important, just as the language subdomain it showed a significant correlation with). Thus, the number of biomarkers will not correspond with the number of included studies in this review.

4. Discussion

4.1 Summary and Interpretation of Main Findings

This literature review aimed to display the intricate relationship between early brain characteristics of EPT and VPT children and their (impaired) language development. Therefore, the research question was which early neuroimaging biomarkers could be associated with (impaired) language development in EPT and VPT children. This literature review synthesized the information of 28 studies on this topic. A large variety of neuroimaging biomarkers was identified, which could be divided in five categories: brain morphometry, brain volumes, white matter microstructure and connectivity, structural abnormalities and miscellaneous.

Brain morphometry and brain volumes showed to be the most promising neuroimaging biomarkers for language development in both EPT and VPT children. For EPT infants, all studies on these types of biomarkers yielded significant results. The characteristics of prominent sulci and volumes of major tissue types all significantly correlated with language on the BSID-III around 30 months CA. Brain morphometry was also investigated in VPT children, but on a higher level. Brain morphometric parameters consisted of cortical thickness, gyrification index, inner cortical curvature, surface area and sulcal depth. Infants with high and low language scores could not be distinguished based on their gyrification indices, but all other parameters had prognostic value for language. Such a direct connection was not found for brain volumes. The association of the major tissue type volumes (cortical gray matter, deep gray matter and white matter) with language reached significance in most cases, but regional volumetric analyses were less successful in correlating specific brain structures, like the cerebellum, thalamus, or globus pallidus, with language. The results were usually either insignificant or inconclusive.

This contrast between major tissue types and brain regions is not surprising, because brain growth does not develop linearly. Brain tissues and structures all have unique developmental trajectories, since growth speed depends on tissue type and region (Thompson et al., 2020). Gray and white matter growth stabilizes around 2 years of age, while the growth trajectories of various brain structures, like the thalamus and cerebellum, take considerably longer. These (sub)cortical structures continue to develop during childhood and even exhibit developmental changes in adolescence. Thus, the maturation of the major tissue types happens faster, since they grow exponentially. The maturation of these tissue types is finished at an earlier age than the development of specific brain structures, which can probably be attributed to their deeper location within the brain. The peak volume of these structures is usually reached between 5 and 9 years (Betlehem et al., 2022; Conte et al., 2024; Wierenga et al., 2014). This difference in volumetric maturation could have influenced the correlations. Language instruments were usually assessed at 2 years (CA). This corresponds with the final volumetric stage of most major tissue types, while brain structures are still developing at this time. This may be the reason why correlations between the major tissue type volumes and language outcomes were easier to capture than correlations between the volumes of various brain structures and language outcomes (i.e., slower maturation may obscure potential relationship with language).

Moreover, individual brain structures show steeper volumetric growth curves than major tissue types. The cerebellum doubles qua volumetric size in the first three months of postnatal life, while white matter increases only by 11% in the first year of life, for instance. This implies that white matter may already be quite close to its target volume around birth (Holland et al., 2014; Knickmeyer et al., 2008). Therefore, EPT or VPT children who experience neurodevelopmental impairments can probably not rely on the catch-up growth and compensatory mechanisms of white matter (and the other tissue types) during the first years of life, on its turn revealing significant connections between white matter and language scores at a later age. After all, white matter volume was the best predictor of all brain tissues and regions: it was consistently and strongly associated with language outcomes in four separate subdomains, namely expressive and receptive language, grammar and semantics.

A remarkable result was found regarding whiter matter integrity (microstructure and connectivity). In EPT children, white matter connectivity had significant prognostic value for language outcomes, but white matter microstructure did not. This dissociation was still partly visible for VPT children, but it had dissolved a bit. However, no firm conclusions can be drawn, since a larger number of studies examined white matter microstructure compared to white matter connectivity. In general, white matter microstructure and connectivity was a weaker biomarker than brain morphometry and volumes. This conflicts with Stipdonk et al. (2018), who found DTI metrics to be more reliable predictors than brain volumes. This difference could again be explained by the age of the population at the MRI scan. Stipdonk et al. (2018) included studies with populations up to 17 years of age. Neuroimaging took place at that age as well. Reduced myelination and the lack of axonal packing at birth could have distorted the possible relationship between microstructural properties and language (Lebel & Deoni, 2018).

Structural MRI abnormalities are probably not exhaustive enough to function as an independent biomarker of language: the majority of studies that investigated this biomarker category could not find an association between abnormality and language scores (see **Table 5**). In a similar literature review, the predictive power of these structural brain injuries was also weak (Stipdonk et al., 2018). This could be explained by the strict exclusion criterion of children with neurological disorders and severe brain injuries. Prematurity often goes hand in hand with these kinds of morbidities (Garbi et al., 2022). Hence, the cohort populations of the included studies were rather small and perhaps a bit biased, since only few children received high brain abnormality scores. This may have resulted in a lack of statistical power for this neuroimaging biomarker. In contrast, studies about miscellaneous predictors, such as fMRI or EEG, had sufficient statistical power to detect significant differences in brain features between preterm children at high and low risk for a language deficit.

4.2 Clinical Implications

The aim of this study was to identify EPT and VPT children who are at an increased risk for language impairment with neuroimaging biomarkers, so targeted interventions can start on time. The data in this review suggest that the macrostructural properties of the brain bear the most prognostic potential. It is recommended that preterm infants undergo routine monitoring from birth, including the performance of an MRI scan. This should become a standardized procedure, as it allows for the extraction of various relevant metrics or parameters (e.g., brain volumes, cortical thickness, sulcal depth, etc.). These metrics or parameters provide information about the language development of preterm children, since in this review they showed multiple significant associations with language outcomes at a later age. When confirmed by other studies, a screening tool could be set up based on brain morphometry and volumes. This will enable early identification of preterm children that are at increased risk for language impairment at a later age. Targeted therapies and interventions can quickly respond to this by offering early help to high-risk children, to mitigate the negative impact of prematurity and its associated brain alterations on language development. This will not only improve their language skills, but it can also boost their self-esteem, social functioning and overall academic performance (Arockia et al., 2024).

4.3 Strengths and Limitations

The strength of this review is that it contains a rich overview of studies that investigated two rather complex topics in EPT and VPT children: the brain and language. Language impairment is quite common in preterm children and appears to be the largest developmental difficulty in VPT children. However, it is frequently overshadowed by the available information on motor and cognitive deficits in this population (Pissara et al., 2023; Sansavini et al., 2021). This review has delved deep into language and even considered various subdomains of language. In addition, it only included longitudinal studies. Longitudinal information on brain maturation is scarce because of inherent difficulties (especially for preterm infants), while this information could be beneficial for the design of appropriate interventions (Torres-González et al., 2024).

A possible limitation of this scoping review could be the heterogeneity in studies. This may explain the inconsistency in the results, predominantly for the categories structural abnormalities and white matter microstructure and connectivity. To illustrate, some studies made use of a 3Tesla MRI scanner (n = 12), but other studies only used a 1.5Tesla scanner (n = 11). In general, studies that were recently published used a 3Tesla scanner, but that was not always the case. Unfortunately, 1.5Tesla is more prone to scanner artifacts and scans have lower spatial resolution due to a reduced image quality (Graves, 2021). However, this literature review has produced an extensive overview of all studies on this topic, as no studies were rejected based on formal requirements for MRI data.

We tried to minimize the impact of the heterogeneity of studies by splitting the results in two birth groups, as a previous literature review pointed to GA as a profound factor causing conflicting results (Stipdonk et al., 2018). Results were quite consistent across birth groups. However, in this review there were no specific requirements for the age at which the language assessments were conducted or for the language instruments used. Age at language assessment is likely an important factor to consider. When all included studies were split into two groups based on age at language assessment (younger vs. equal to/older than 3 years), preliminary analyses suggest different patterns of results may be observed for the two groups: there was an even number of significant and insignificant biomarkers for the older group, while there were twice as many significant studies than insignificant ones for the younger group. This could indicate that there might be a tipping point (i.e., a certain age) during brain development, from which language does not correlate with a specific brain characteristic or region anymore, because it has developed in an efficient full-fledged system that makes use of the entire brain to process and produce language. It would be interesting to investigate this developmental window more closely and see if this tipping point is linked to the critical period of language.

Another limitation is the broad spectrum of language assessment instruments that were used to assess the language competence of the preterm children. Most studies used standardized tests, but sometimes educational achievements were interpreted as language outcomes [**12**]. Furthermore, some of these tests are criticized for not being in-depth enough to test actual language skills and for being a poor predictor of future developmental abilities. This is mainly the case for the BSID, which was used by 16 of the 28 studies (Anderson & Burnett, 2017; Kvestad et al., 2022). Some of the included studies used a test measuring intellectual functioning to test overall neurodevelopmental functioning of preterm children. The verbal scale would then represent language skills. However, according to Stipdonk et al. (2020), there is not such a one-to-one relation between verbal IQ and language scores.

4.4 Future Research Directions

This review tried to shed light on early neuroimaging biomarkers that could aid in the identification of EPT or VPT children at risk for language impairment later in life. We found that biomarkers from the categories brain morphometry and volumes had the highest prognostic value, especially for oral language. Further research into this topic is necessary to confirm these findings and to test the prognostic value of these two types of neuroimaging biomarkers for other language categories as well (i.e., phonological awareness, verbal fluency and written language). Structural abnormalities and white matter integrity did not show a consistent relationship with language in preterm children. Although white matter abnormalities are very common in preterm children, the qualitative scoring of these abnormalities was barely associated with a language deficit. On the other hand, studies that approached these abnormalities quantitatively with an objective algorithm always yielded significant results [**8**; **14**; **24**]. This pattern was also visible for other biomarker categories. Quantitative research designs that implemented machine learning were quite successful in detecting biomarkers of a (probable) language deficit in young children for the categories miscellaneous predictors and white matter microstructure and connectivity. Therefore, future studies are encouraged to make use of artificial intelligence, higher-order techniques and deep learning models in discovering potential biomarkers, since the studies that used this approach nearly always yielded high accuracies and significant results [**1**; **6**; **8**; **15**].

Moreover, studies that went beyond the golden standard (MRI) to explore potential biomarkers of language development, were quite successful in doing so. Four studies were included in the category miscellaneous predictors and three of them found significant results [**2**; **3**; **6**; **8**]. Future studies that aspire to investigate the neuroimaging biomarkers of language development must not solely focus on diffusion or structural MRI. It could also be advantageous to combine several neuroimaging methods into one multimodal design [**8**], since this might lead to better prognoses of neurodevelopmental impairments. Besides, future studies are recommended to adopt a novel perspective by investigating the prognostic value of biomarkers from other fields of interest, such as biophysiological or environmental biomarkers. For example, two promising candidates for biophysiological biomarkers seem placental microorganisms (Scott Tomlinson et al., 2020) or growth hormones (Scratch et al., 2015). The environmental factor maternal education also seems worth investigating (Howard et al., 2011), as it was often included as a covariate in the multivariable statistical models of the included studies and was an independent predictor of language development.

It should also be taken into account that this review included a sheer variety of studies. Future review studies are advised to use stricter inclusion criteria to enhance comparability between studies. For instance, they should not only to pay attention to the publication date, but also to the details on the MRI data. It would also be advantageous to stratify studies according to age at language assessment, since this is probably an important factor. The inclusion of studies using a similar kind of MRI scanner or study protocol in general, will facilitate the comparisons between studies.

Finally, this review investigated the language skills of EPT and VPT children. Premature birth often results in a low birth weight. The children of the analyzed studies also all had very low birth weights, which was sometimes even used as an (additional) inclusion criterion. This complicates the establishment of a clear causal relationship between prematurity, neuroimaging at TEA and language development. It would be interesting for future studies to conduct research on preterm children with normal birth weights,[6] to see if these children experience similar kinds and the same number of language problems as premature children with low birth weights and present comparable brain abnormalities. This kind of research could clarify whether a language deficit can be linked to a low birth weight or to prematurity, and which brain parameters could be responsible for this deficit.

5. Conclusion

The third trimester functions as an important window in which rapid brain development takes place, which underlies various higher-order neurodevelopmental processes. This review has demonstrated that the blueprint of future language achievements might already be present in EPT and VPT children at birth. Our results show interesting opportunities for the use of neuroimaging biomarkers to predict language outcomes in EPT and VPT children. Brain morphometry and volumes were the most promising neuroimaging biomarkers. Structural abnormalities and white matter integrity were, however, not reliable enough. It could be advantageous to integrate multiple modalities into one research design or to use neuroimaging methods beyond the default MRI to detect biomarkers. Future review studies should synthesize data more carefully with stricter inclusion criteria, allowing for a more selective group of studies and more accurate comparisons between studies. All in all, the future of detecting neuroimaging biomarkers looks bright, particularly with the development of machine learning models and deep learning algorithms. Hopefully it will accelerate the identification of high-risk children and the start of targeted interventions to reach the child's full potential.

[6] These children do exist (see Paneth et al. [1986] or Young et al. [2012])

References

Aarnoudse-Moens, C.S.H., Weisglas-Kuperus, N., Van Goudoever, J.B., & Oosterlaan, J. (2009). Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics*, *124*, 717-728. https://doi.org/10.1542/peds.2008-2816

Anderson, P.J., & Burnett, A. (2017). Assessing developmental delay in early childhood – concerns with the Bayley-III scales. *The Clinical Neuropsychologist*, *31*(2), 371-381. https://doi.org/10.1080/13854046.2016.1216518

[17] Anderson, P.J., Treyvaud, K., Neil, J.J., Cheong, J.L.Y., Hunt, R.W., Thompson, D.K., Lee, K.J., Doyle, L.W., & Inder, T.E. (2017). Associations of newborn brain MRI with long-term neurodevelopmental impairments in very preterm children. *Journal of Pediatrics*, *187*, 58-65. https://doi.org/1 0.1016/j.jpeds.2017.04.059

Arockia, A.S., Hema, V.H., & Ashok, J. (2024). Early interventions and their impact on social skills and academic performance in children with specific learning disabilities. *Frontiers in Health Informatics*, *13*(3), 1861-1877.

Auris Audiologisch Centrum. (n.d.). *WISC-III-NL*. Retrieved 24 October, 2024, from https://auris.nl/wp-content/uploads/wisc-iii-nl.pdf

Barfield, W.D. (2018). Public health implications of very preterm birth. *Clinics in Perinatology*, *45*(3), 565-577. https://doi.org/10.1016/j.clp.2018.05.007

[1] Barnes-Davis, M., Williamson, B.J., Kline, J.E., Kline-Fath, B.M., Tkach, J., He, L., Yuan, W., & Parikh, N.A. (2024). Structural connectivity at term equivalent age and language in preterm children at 2 years corrected. *Brain Communications*, fcae126. 0.1016/j.jpeds.2017.04.059

Barnes-Davis, M., Williamson, B.J., Merhar, S.L., Holland, S.K., & Kadis, D.S. (2020). Extremely preterm children exhibit altered cortical thickness in language areas. *Scientific Reports*, *10*, 10824. https://doi.org/10.1038/s41598-020-67662-7

Biasiucci, A., Franceschiello, B., & Murray, M.M. (2019). Electroencephalography. *Current Biology*, *29*(3), 80-85. https://doi.org/10.1016/j.cub.2018.11.052

Balasundaram, P., & Avulakunta, I.D. (2022). *Bayley Scales of Infant and Toddler Development*. StatPearls publishing.

Betlehem, R.A.I., Seidlitz, J., White, S.R., Vogel, J.W., Anderson, K.M., Adamson, C., Adler, S., Alexopoulos, G.S., Anagnostou, E., Areces-Gonzalez, A., Astle, D.E., Auyeung, B., Ayub, M., Bae, J., Ball, G., Baron-Cohen, S., Beare, R., Bedford, S.A., Benegal, V. … & Zuo, X.N. (2022). Brain charts for the human lifespan. *Nature*, *604*(7906), 525-533. https://doi.org/10.1038/s41586-022-04554-y

Blencowe, H., Lee, A.C.C., Counsens, S., Bahalim, A., Narwall, R., Zhong, N., Chou, D., Say, L., Modi, N., Katz, J., Vos, T., Marlow, N., & Lawn, J.E. (2013). Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels for 2010. *Pediatric Research*, *74*(1), 17-34. https://doi.org/ 10.1038/pr.2013.204

Bonifacci, P., Cangelosi, M., & Bellochi, S. (2024). Oral language predictors of word reading and spelling: A cross-linguistic comparison in bilingual and monolingual children. *Journal of Experimental Child Psychology*, *243*, 105926. https://doi.org/10.1016/j.jecp.2024.105926 0022-0965

Brósch-Fohraheim, N., Fuiko, R., Marschik, P.B., & Resch, B. (2019). The influence of preterm birth on expressive vocabulary at the age of 36 to 41 months. *Medicine*, *98*(6), e14404. https://doi.org/10.1097/MD.0000000000014404

Bruns, N., Blumenthal, S., Meyer, I., Klose-Verschuur, S., Felderhoff-Müser, U., & Müller, H. (2017). Application of an amplitude-integrated EEG monitor (cerebral function to monitor) to neonates. *Journal of Visualized Experiments*, *127*, e55985. https://doi.org/10.3791/55985

Brydges, C.R., Landes, J.K., Reid, C.L., Campbell, C., French, N., & Anderson, M. (2018). Cognitive outcomes in children and adolescents born very preterm: a meta-analysis. *Developmental Medicine & Child Neurology*, *60*(5), 452-468. https://doi.org/10.1111/dmcn.13685

Cho, H.J., Jeong, H., Park, C-A., Son, D.W., & Shim, S-Y. (2022). Altered functional connectivity in children born very preterm at school age. *Scientific Reports*, *12*, 7308. https://doi.org/10.1038/s41598-022-11184-x

Choi, U-S., Shim, S-Y, Cho, H.J., & Jeong, H. (2024). Association between cortical thickness and cognitive ability in very preterm school-age children. *Scientific Reports*, *14*, 2424. https://doi.org/10.1038/s41598-024-52576-5

Clark, K.A., Nuechterlein, K.H., Asarnow, R.F., Hamilton, L.S., Philips, O.R., Hageman, N.S., Woods, R.P., Alger, J.R., Toga, A.W., & Narr, K.L. (2011). Mean diffusivity and fractional anisotropy as indicators of disease and genetic liability to schizophrenia. *Journal of Psychiatric Research*, *45*(7), 980-988. https://doi.org/10.1016/j.jpsychires.2011.01.006

Cole, T.J., Statnikov Y., Santhakumaran, S., Pan, H., & Modi, N. (2014). Birth weight and longitudinal growth in infants born below 32 weeks' gestation: A UK population study. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, *99*(1), 34-40. https://doi.org/ 10.1136/archdischild-2012-303536

Conte, S., Zimmerman, D., & Richards, J.E. (2024). White matter trajectories over the lifespan. *PLoS ONE*, *19*(5), e0301520. https://doi.org/10.1371/journal.pone.0301520

Coughlan, S., Quigley, J., & Nixon, E. (2023). Preterm birth and expressive language development across the first 5 years of life: A nationally-representative longitudinal path analysis. *Early Childhood Research Quarterly*, *65*, 417-427. https://doi.org/10.1016/j.ecresq.2023.08.004

De Kievit, J.F., Zoetebier, L., Van Elburg, R.M., Vermeulen, R.J., & Oosterlaan, J. (2012). Brain development of very preterm and very low-birthweight children in childhood and adolescence: A meta-analysis. *Developmental Medicine & Child Neurology, 54*(4), 313-323. https://doi.org/10.1111/j.1469-8749.2011.04216.x

Dibble, M., Ang, J.Z., Mariga, L., Molloy, E.J., & Bokde, A.L.W. (2020). Diffusion tensor imaging in very preterm, moderate-late preterm and term-born neonates: A systematic review. *Journal of Pediatrics*, *232*, 48-58. https://doi.org/10.1016/j.jpeds.2021.01.008

Drommelschmidt, K., Mayrhofer, T., Hüning, B., Stein, A., Foldyna, B., Schweiger, B., Felderhoff-Müser, U., & Sirin, S. (2024). Incidence of brain injuries in a large cohort of very preterm and extremely preterm infants at term-equivalent age: Results of a single tertiary neonatal care center over 10 years. *European Radiology*, *34*, 5239-5249. https://doi.org/10.1007/s00330-024-10592-z

[11] Dubner, S.E., Rose, J., Bruckert, L., Feldman, H.M., & Travis, K.E. (2020). Neonatal white matter tract microstructure and 2-year language outcomes after preterm birth. *NeuroImage: Clinical*, *28*, 102446. https://doi.org/10.1016/j.nicl.2020.102446

Engelhardt, E., Inder, T.E., Alexopoulos, D., Dierker, D.L., Hill, J., Van Essen, D., & Neil, J.J. (2015). Regional impairments of cortical folding in premature infants. *Annals of Neurology*, *77*(1), 154-162. https://doi.org/ 10.1002/ana.24313

Evans, A.G., Morgan, M.D., Aiken, B.A., Assi, P.E., Joesph, J.T., Kesayan, T., Mioton, L.M., Esteve, I.V.M., Hill, J.B., Thayer, W.P., & Al Kassis, S. (2023). Can diffusion tensor imaging apparent diffusion coefficient diagnose carpal tunnel syndrome? A systematic review and meta-analysis. *HAND*, *18*(1), 91-99. https://doi.org/10.1177/15589447221096706

[7] Garbi, A., Sorin, G., Coze, S., Resseguier, N., Brévaut-Malaty, Marret, S., Muller, J-B., Tosello, B., & Gire, C. (2022). Predictive value of brain MRI at term-equivalent age in extremely preterm children on neurodevelopmental outcome at school-age. *Brain Imaging and Behavior*, *16*, 878-887. https://doi.org/10.1007/s11682-021-00559-9

Gaser, C. (2016). Structural MRI: morphometry. In M. Reuter, & C. Montag (Eds.), *Neuroeconomics, Studies in Neuroscience, Psychology and Behavioral Economics* (pp. 399-409). Springer-Verlag. https://doi.org/10.1007/978-3-642-35923-1_21

Gilard, V., Tebani, A., Bekri, S., & Marret, S. (2020). Intraventricular hemorrhage in very preterm infants: A comprehensive review. *Journal of Clinical Medicine*, *9*, 2447. https://doi.org/10.3390/jcm9082447

Glass, H.C., Wusthoff, C.J., & Shellhaas, R.A. (2013). Amplitude integrated EEG: the child neurologist's perspective. *Journal of Child Neurology*, *28*(10), 1342-1350. https://doi.org/10.1177/0883073813488663

Gorham, L.S., Latham, A.R., Alexopoulos, D., Kenley, J.K., Iannopollo, E., Lean, R.E., Loseille, D., Smyser, T.A., Neil, J.J., Rogers, C.E., Smyser, C.D., & Garcia, K. (2024). Children born very preterm experience altered cortical expansion over the first decade of life. *Brain Communications,* fcae318. https://doi.org/10.1093/braincomms/fcae318

Govaert, P., Trizuli, F., & Dudink, J. (2020). The developing brain by trimester. In E.A.P. Steegers, M.J. Cipolla & E.C. Millers (Eds.), *Handbook of Clinical Neurology, Neurology and Pregnancy*: *Pathophysiology and Patient Care* (3rd edition, Vol. 171, pp. 245-289). Elsevier. https://doi.org/10.1016/B978-0-444-64239-4.00014-X

Gozdas, E., Parikh, N.A., Merhar, S.L., Tkach, J.A., He, L., & Holland, S.K. (2018). Altered functional network connectivity in preterm infants: antecedents of cognitive and motor impairments? *Brain Structure and Function*, *223*(8), 3665-3680. https://doi.org/10.1007/s00429-018-1707-0

Graves, M.J. (2022). 3T: the good, the bad and the ugly. *British Journal of Radiology, 95*(1130), 20210708. https://doi.org/10.1259/bjr.20210708

Guarini, A., Bonifacci, P., Tobia, V., Alessandroni, R., Faldella, G., & Sansavini, A. (2019). The profile of very preterm children on academic achievement. A cross-population comparison with children with specific learning disorders. *Research in Developmental Disabilities*, *87*, 54-63. https://doi.org/10.1016/j.ridd.2019.02.001

Hadayaa, L., & Nosarti, C. (2020). The neurobiological correlates of cognitive outcomes in adolescence and adulthood following very preterm birth. *Seminars in Fetal and Neonatal Medicine*, *25*, 101117. https://doi.org/10.1016/j.siny.2020.101117

Harcourt Assessment. (n.d.). *The NEPSY – Second Edition*. Retrieved 24 October, 2024, from https://www.pearsonclinical.ca/content/dam/school/global/clinical/us/assets/nepsy-ii/nepsy-ii-design-and-purpose.pdf

[8] He, L., Li, H., Chen, M., Wang, J., Altaye, M., Dillman, J.R., & Parikh, N.A. (2021). Deep multimodal learning from MRI and clinical data for early prediction of neurodevelopmental deficits in very preterm infants. *Frontiers in Neuroscience*, *15*, 753033. https://doi.org/ 10.3389/fnins.2021.753033

[24] He, L., & Parikh, N.A. (2013). Atlas-guided quantification of white matter signal abnormalities on term-equivalent age MRI in very preterm infants: Findings predict language and cognitive development at two years of age. *PLoS ONE*, *8*(12), e85475. https://doi.org/ 10.1371/journal.pone.0085475

Holland, D., Chang, L., Ernst, T.M., Curran, M., Buchthal, S.D., Alicata, D., Skranes, J., Johansen, H., Hernandez, A., Yamakawa, R., Kuperman, J.K., & Dale, A.M. (2014). Structural growth trajectories and rates of change in the first 3 months of infant brain development. *JAMA Neurology*, *71*(10), 1266-1274. https://doi.org/10.1001/jamaneurol.2014.1638

Howard, K., Roberts, G., Lim, J., Lee, K.J., Barre, N., Treyvaud, K., Cheong, J., Hunt, R.W., Inder, T.E., Doyle, L.W., & Anderson, P.J. (2011). Biological and environmental factors as predictors of language skills in very preterm children at 5 years of age. *Journal of Developmental and Behavioral Pediatrics*, *32*(3), 239-249. https://doi.org/10.1097/DBP.0b013e31820b7882

[12] Jansen, L., Peeters-Scholte, C., Wiggers-de Bruine, S., Van den Berg-Huysmans, A., Van Klink, J., Van Steenis, A., Rijken, M., Vermeiren, R., & Steggerda, S. (2020). Classroom-evaluated school performance at nine years of age after very preterm birth. *Early Human Development*, *140*, 104834. https://doi.org/10.1016/j.earlhumdev.2019.104834

Jois, R.S. (2019). Understanding long-term neurodevelopmental outcomes of very and extremely preterm infants. *Australian Journal of General Practice*, *48*(1-2), 26-32. https://doi.org/10.31128/AJGP-04-18-4545.

Karolis, V.R., Froudist-Walsh, S., Kroll, J., Brittain, P.J., Tseng, C-E.J., Nam, K-W., Reinders, A.A., Murray, R.M., Williams, S.C.R., Thompson, P.M., & Nosarti, C. Volumetric grey matter alterations in adolescents and adults born very preterm suggest accelerated brain maturation. *NeuroImage*, *163*, 379-389. https://doi.org/10.1016/j.neuroimage.2017.09.039

Kelly, C.E., Shaul, M., Thompson, D.K., Mainzer, R.M., Yang, J.Y.M., Dhollander, T., Cheong, J.L.Y., Inder, T.E., Doyle, L.W., & Anderson, P.J. (2023). Long-lasting effects of very preterm birth on brain structure in adulthood: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, *147*, 105082. https://doi.org/10.1016/j.neubiorev.2023.105082

Kelly, C.E., Thompson, D.K., Adamson, C.L., Ball, G., Dhollander, T., Beare, R., Matthews, L.G., Alexander, B., Cheong, J.L.Y., Doyle, L.W., Anderson, P.J., & Inder, T.E. (2024). Cortical growth from infancy to adolescence in preterm and term-born children. *BRAIN*, *147*, 1526-1538. https://doi.org/10.1093/brain/awad348

[20] Kersbergen, K.J., Leroy, F., Isgum, I., Groenendaal, F., De Vries, L.S., Claessesn, N.H.P., Van Haastert, I.C., Moeskops, P., Fischer, C., Mangin, J-F., Viergever, M.A., Dubois, J., & Benders, M.J.N.L. (2016). Relation between clinical risk factors, early cortical changes and neurodevelopmental outcome in preterm infants. *NeuroImage, 142*, 301-310. https://doi.org/10.1016/j.neuroimage.2016.07.010

Kesler, S.R., Reiss, A.L., Vohr, B., Watson, C., Schneider, K.C., Katz, K.H., Maller-Kasselman, J., Silbereis, J., Constable, R.T., Makuch, R.W., & Ment, L.R. (2008). Brain volume reductions within multiple cognitive systems in male preterm children at age twelve. *Journal of Pediatrics*, *152*(4), 513-520. https://doi.org/10.1016/j.jpeds.2007.08.009

[18] Keunen, K., Benders, M.J., Leemans, A., Fieret-Van Stam, P.C., Scholtens, L.H., Viergever, M.A., Kahn, R.S., Groenendaal, F., De Vries, L.S., & Van den Heuvel, M.P. (2017). White matter maturation in the neonatal brain is predictive of school age cognitive capacities in children born very preterm. *Developmental Medicine & Child Neurology*, *59*(9), 939-946. https://doi.org/10.1111/dmcn.13487

Kim, H., Ahn, J-H., Lee, J.Y., Jang, Y.H., Kim, Y-E., Kim, J.I., Kim, B-N., & Lee, H.J. (2022). Altered cerebral curvature in preterm infants is associated with the common genetic variation related to autism spectrum disorder and lipid metabolism. *Journal of Clinical Medicine*, *11*, 3135. https://doi.org/10.3390/ jcm11113135

Kline, J.E., Illapani, V.S.P., He, L., Altaye, M., & Parikh, N.A. (2019). Retinopathy of prematurity and bronchopulmonary dysplasia are independent antecedents of cortical maturational abnormalities. *Scientific Reports*, *9*, 19679. https://doi.org/10.1038/s41598-019-56298-x

[13] Kline, J.E., Illapani, V.S.P., He, L., Altaye, M., Logan, J.W., & Parikh, N.A. (2020). Early cortical maturation predicts neurodevelopment in very preterm infants. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, *105*(5), 460-465. https://doi.org/10.1136/archdischild-2019-317466

Knickmeyer, R.C., Gouttard, S., Kang, C., Evans, D., Wilber, K., Smith, J.K., Hamer, R.W., Lin, W., Cerig, G., & Gilmore, J.H. (2008). A structural MRI study of human brain development from birth to 2 years. *The Journal of Neuroscience*, *28*(47), 12176-12182. https://doi.org/10.1523/JNEUROSCI.3479-08.2008

Konzett, K., Riedl, D., Blassnig-Ezeh, A., Gang, S., & Simma, B. (2024). Outcome in very preterm infants: a population-based study from a regional center in Austria. *Frontiers in Pediatrics*, 12:1336469. https://doi.org/10.3389/fped.2024.1336469

Kovachy, V.N., Adams, J.N., Tameresis, J.S., & Feldman, H.M. (2015). Reading abilities in school-aged preterm children: A review and meta-analysis. *Developmental Medicine & Child Neurology*, *57*(5), 410-419. https://doi.org/10.1111/dmcn.12652

Kroll, J., Karolis, V., Brittain, P.J., Tseng, C-E.J., Froudist-Walsh, S., Murray, R.M., & Nosarti, C. (2017). Real-life impact of executive function impairments in adults who were born very preterm. *Journal of the International Neuropsychological Society*, *23*, 381-389. https://doi.org/10.1017/S1355617717000169

Kunnari, S., Ylihervaa, A., Paavolaa, L., & Peltoniemib, O.M. (2012). Expressive language skills in Finnish two-year-old extremely- and very-low-birth-weight preterm children. *Folia Phoniatrica et Logopaedica*, *64*, 5-11. https://doi.org/10.1159/000328641

Kvanta, H., Bolk, J., Broström, L., Nosko, D., Fernández de Gamarara-Oca, L., Padilla, N., & Ådén, U. (2024). Language performance and brain volumes, asymmetry, and cortical thickness in children born extremely preterm. *Pediatric Research*, *95*, 1070-1079. https://doi.org/10.1038/s41390-023-02871-0

Kvestad, I., Hysing, M., Ranjitkar, S., Shrestha, M., Ulak, M., Chandyo, R.K., & Strand, T.A. (2022). The stability of the Bayley scales in early childhood and its relationship with future intellectual abilities in a low to middle income country. *Early Human Development*, *170*, 105610. https://doi.org/10.1016/j.earlhumdev.2022.105610

Kwon, S.H., Scheinost, D., Lacadie, B., Sze, G., Schneider, K.C., Dai, F., Contable, R.T., & Ment, L.R. (2015). Adaptive mechanisms of developing brain: cerebral lateralization in the prematurely-born. *Neuroimage*, *108*, 144-150. https://doi.org/10.1016/j.neuroimage.2014.12.032

Labus, J.S., Tun, G., Kilpatrick, L.A., Rao, S.S.C., Mayer, E.A., & Tillish, K. (2020). Neuroimaging and biomarkers in functional gastrointestinal disorders: What the scientists and clinicians need to know about basic neuroimaging, biomarkers, microbiome, gut and brain interactions. In S.S.C. Rao, Y.Y. Lee, & U.C. Ghoshal (Eds.), *Clinical and Basic Neurogastroenterology and Motility* (pp. 31-61). Academic Press. https://doi.org/10.1016/B978-0-12-813037-7.00003-0

Lammertink, F., Vinkers, C.H., Tataranno, ML, & Benders, M.J.N.L. (2021). Premature birth and developmental programming: Mechanisms of resilience and vulnerability. *Frontiers in Psychiatry, 11*, 531571. https://doi.org/10.3389/fpsyt.2020.531571

Larroque, B., Bréart, G., Kaminski, M., Dehan, M., André, M., Burguet, A., Grandjean, H., Ledésert, B., Lévêque, C., Maillard, F., Matis, J., Rozé, J.C., & Truffert, P. (2004). Survival of very preterm infants: Epipage, a population based cohort study. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, *89*, 139-144. https://doi.org/10.1136/adc.2002.020396

Lebel, C., & Deoni, S. (2018). The development of brain white matter microstructure. *NeuroImage*, *182*, 207-218. https://doi.org/10.1016/j.neuroimage.2017.12.097

[9] Lee, H.J., Kwon, H., Kim, J.I., Lee, J.Y., Lee, J.Y., Bang, S., & Lee, J-M. (2021). The cingulum in very preterm infants relates to language and social-emotional impairment at 2 years of term-equivalent age. *NeuroImage: Clinical*, *29*, 102528. https://doi.org/10.1016/j.nicl.2020.102528

Levy, O., Kenett, Y.N., Oxenberg, O., Castro, N., De Deyne, S., Vitevitch, M.S., & Havlin, S. (2021). Unveiling the nature of interaction between semantics and phonology in lexical access based on multilayer networks. *Scientific Reports*, *11*, 14479. https://doi.org/10.1038/s41598-021-93925-y

Liu, C.H. (2016). Anatomical, functional and molecular biomarker applications of magnetic resonance neuroimaging. *Future Neurology*, *10*(1), 49-65. https://doi.org/10.2217/FNL.14.60

Liu, L., Oza, S., Hogan D., Chu, Y., Perin, J., Zhu, J., Lawn, J.E., Cousens, S., Mathers, C., & Black, R.E. (2016). Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. *The Lancet*, *388*, 3027-3035. https://doi.org/10.1016/ S0140-6736(16)31593-8

Locke, A., & Kanekar, S. (2022). Imaging of premature infants. *Clinics in Perinatology*, *49*, 641-655. https://doi.org/10.1016/j.clp.2022.06.001

Luu, T.M., Vohr, B.R., Schneider, K.C., Katz, K.H., Tucker, R., Allan, W.C., & Ment, L.R. (2009). Trajectories of receptive language development from 3 to 12 years in very preterm children. *Pediatrics*, *124*91), 333-341. https://doi.org/10.1542/peds.2008-2587

Makropoulos, A., Aljabar, P., Wright, R., Hüning, B., Merchant, N., Arichi, T., Tusor, N., Hajnal, J.V., Edwards, A.D., Counsell, S.J., & Rueckert, D. (2016). Regional growth and atlasing of the developing human brain. *NeuroImage*, *125*, 456-478. https://doi.org/10.1016/j.neuroimage.2015.10.047

Martin, K.C., Ketchabaw, W.T., & Turkeltaub, P.E. (2022). Plasticity of the language system in children and adults. *Handbook Clinical Neurology*, *184*, 397-414. https://doi.org/10.1016/B978-0-12-819410-2.00021-7.

[16] Matthews, LG., Inder, T.E., Pascoe, L., Kapur, K., Lee, K.J., Monson, B.B., Doyle, L.W., Thompson, D.K., & Anderson, P.J. (2018). *Cerebellum*, *17*(5), 610-127. https://doi.org/ 10.1007/s12311-018-0946-1

Mayo Clinic. (2022, June 3). *Pregnancy week by week.* https://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/fetal-development/art-20045997#:~:text=Week%2032%3A%20Baby%20practices%20breathing&text=The%20layer%20of%20soft%2C%20downy,4%20pounds%20(1%2C700%20grams).

Milankov, V., Golubovic, S., Krstic, T., & Golubovic, S. (2021). Phonological awareness as the foundation of reading acquisition in students reading in transparent orthography. *International Journal of Environmental Research and Public Health*, *18*, 5440. https://doi.org/10.3390/ijerph18105440

[21] Monson, B.B., Anderson, P.J., Matthews, L.G., Neil, J.J., Kapur, K., Cheong, J.LY., Doyle, L.W., Thompson, D.K., & Inder, T.E. (2016). Examination of the pattern of growth of cerebral tissue volumes from hospital discharge to early childhood in very preterm infants. *JAMA Pediatrics*, *170*(8), 772-779. https://doi.org/10.1001/jamapediatrics.2016.0781

Montagna, A., Karolis, V., Batalle, D., Counsell, S., Rutherford, M., Arulkumaran, S., Happe, F., Edwards, D., & Nosarti, C. (2020). ADHD symptoms and their neurodevelopmental correlates in children born very preterm. *PLoS ONE*, *15*(3), e0224343. https://doi.org/10.1371/journal.pone.0224343

Nguyen, T-N-N., Spencer-Smith, M., Haebich, K.M., Burnett, A., Scratch, S.E., Cheong, J.L.Y., Doyle, L.W., Wiley, J.F., & Anderson, P.J. (2018[a]). Language trajectories of children born very preterm and full term from early to late childhood. *Journal of Pediatrics*, 202:86-91.e1. https://doi.org10.1016/j.jpeds.2018.06.036

Nguyen, T-N-N., Spencer-Smith, M., Zannino, D., Burnett, A., Scratch, S.E., Pascoe, L., Ellis, R., Cheong, J., Thompson, D., Inder, T., Doyle, L.W., Anderson, P.J. (2018[b]). Developmental trajectory of language from 2 to 13 years in children born very preterm. *Pediatrics, 141*(5), e20172831. https://doi.org/10.1542/peds.2017-2831

[28] Nosarti, C., Walshe, M., Rushe, T.M., Rifkin, L., Wyatt, J., Murray, R.M., & Allin, M.P. (2011). Neonatal ultrasound results following very preterm birth predict adolescent behavioral and cognitive outcome. *Developmental Neuropsychology*, *36*(1), 118-135. https://doi.org/10.1080/87565641.2011.540546

Ohuma, E.O., Moller, A-B., Bradley, E., Chakwera, S., Hussain-Alkhateeb, L., Lewin, A., Okwaraji, Y.B., Mahanani, W.R., White Johansson, E., Lavin, T., Estevez Fernandez, D., Gatica Domínguez, G., De Costa, A., Cresswell, J.A., Krasevec, J., Lawn J.E., Blencowe, H., Requejo, J., & Moran, A.C. (2023). National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis. *The Lancet, 402*, 1261-1271. https://doi.org/10.1016/S0140-6736(23)00878-4

[5] Pagnozzi, A.M., Van Eijk, L., Pannek, K., Boyd, R.N., Saha, S., George, J., Bora, S., Bradford, D., Fahey, M., Ditchfield, M., Malhotra, A., Liley, H., Colditz, P.B., Rose, S., & Fripp, J. (2023). Early brain morphometrics from neonatal MRI predict motor and cognitive outcomes at 2-years corrected age in very preterm infants. *NeuroImage*, *267*, 119815. https://doi.org/10.1016/j.neuroimage.2022.119815.

Paneth, N., Wallenstein, S., Kiely, J.L., Snook, C.P., & Susser, M. (1986). Medical care and preterm infants of normal birth weight. *Pediatrics*, *77*(2), 158-166.

Pannek, K., Fripp, J., George, J.M., Fiori, S., Colditz, P.B., Boyd, R.N., & Rose, S.E. (2018). Fixel-based analysis reveals alterations is brain microstructure and macrostructure of preterm-born infants at term equivalent age. *NeuroImage: Clinical*, *18*, 51-59. https://doi.org/10.1016/j.nicl.2018.01.003

[10] Parikh, M.N., Chen, M., Baimah, A., Kline, J., McNally, K., Logan, J.W., Tamm, L., Yeates, K.O., Yuan, W., He, L., & Parikh, N.A. (2021). Diffusion MRI microstructural abnormalities at term-equivalent age are associated with neurodevelopmental outcomes at 3 years of age in very preterm infants. *American Journal of Neuroradiology*, *42*(8), 1535-1542. https://doi.org/ 10.3174/ajnr.A7135

[14] Parikh, N.A., He, L., Illapani, V.S.P., Altaye, M., Folger, A.T., & Yeates, K.O. (2020). Objectively-diagnosed diffuse white matter abnormality at term is an independent predictor of cognitive and language outcomes in infants born very preterm. *Journal of Pediatrics*, *220*, 56-63. https://doi.org/10.1016/j.jpeds.2020.01.034

Pearson Clinical Assessment. (n.d.). *WPPSI-IV-NL | Wechsler Preschool and Primary Scale of Intelligence*. Retrieved 24 October, 2024, from https://www.pearsonclinical.nl/wppsi-iv-nl?srsltid=AfmBOorZUaA2P9T5JFE_qXa01feKpmZvrS8zx3KjHyY-3B6DZpxdwjvB

Pearson Education. (2008). *Technical Report CELF*. Retrieved 24 October, 2024, from https://www.pearsonassessments.com/content/dam/school/global/clinical/us/assets/celf-4/celf-4-technical-report.pdf

[19] Peyton, C., Yang, E., Msall, ME., Adde, L., Støen, R., Fjørtorft, T., Bos, A.F., Einspieler, C., Zhou, Y., Schreiber, M.D., Marks, J.D., & Drobsheyvsky, A. (2017). White matter injury and general movements in high-risk preterm infants. *American Journal of Neuroradiology*, *38*(1), 162-169. https://doi.org/ 10.3174/ajnr.A4955

Pissara, R., Periera-Neto, B., Miragaia, P., Almeida, S., Flor-De-Lima, Fl., & Soares, P. (2023). Predictors of poor neurodevelopmental outcomes of very preterm and very low birth weight infants. *Minerva Pediatrics (Torino)*, *6*. https://doi.org/10.23736/S2724-5276.23.07360-3

Putnick, D.L., Bornstein, M.H., Eryigit-Madzwamuse, S., Wolke, D. (2017). Long-term stability of language performance in very preterm, moderate-late preterm and term children. *Journal of Pediatrics*, *181*, 74-79. https://doi.org/10.1016/j.jpeds.2016.09.006

Quinn, J-A., Munoz, F.M., Gonik, B., Frau, L., Cutland, C., Mallett-Moore, T., Kissou, A., Wittke, F., Das, M., Nunes, T., Pye, S., Watson, W., Ramos, A-M.A., Cordero, J.F., Huang, W-T., Kochar, S., & Buttery, J. (2016). Preterm birth: Case definition & Guidelines for data collection, analysis, and presentation of immunisation safety data. *Vaccine*, *34*, 6047-6056. http://doi.org/10.1016/j.vaccine.2016.03.045

Ranzenberger, L.R., & Snyder, T. (2022). *Diffusion Tensor Imaging*. StatPearls publishing.

Ream, M.A., & Lehwald, L. (2018). Neurologic consequences of preterm birth. *Current Neurology and Neuroscience Reports*, *18*(8), 48. https://doi.org/10.1007/s11910-018-0862-2

[25] Reidy, N., Morgan, A., Thompson, D.K., Inder, T.E., Doyle, L.W., & Anderson, P.J. (2013). Impaired language abilities and white atter abnormalities in children born very preterm and/or very low birth weight. *Journal of Pediatrics*, *162*(4), 719-724. https://doi.org/10.1016/j.jpeds.2012.10.017

[2] Reis, J.D., Hagan, T., Heyne, R., Tolentino-Plata, K., Clarke, R., Brown, L.S., Rosenfeld, C.R., Burchfield, P.J., Caraig, M., & Brion, L.P. (2024). Relationship between ventricular size on latest ultrasonogram and the Bayley scores ≥ 18 months in extremely low gestational age neonates: A retrospective cohort study. *American Journal of Perinatology, 41*, 1409-1416. https://doi.org/ 10.1055/a-2057-7454.

Rogers, C.E., Lean, R.E., Wheelock, M.D., & Smyser, C.D. (2018). Aberrant structural and functional connectivity and neurodevelopmental impairment in preterm children. *Journal of Neurodevelopmental Disorders*, *10*(38), 1-13. https://doi.org/10.1186/s11689-018-9253-x

Rogers, B.P., Morgan, V.L., Newton, T.A., & Gor, J.C. (2007). Assessing functional connectivity in the human brain by fMRI. *Magnetic Resonance Imaging*, *25*(10), 1347-1357. https://doi.org/10.1016/j.mri.2007.03.007

Roufaeil, C., Razak, A., & Malhotra, A. Cranical ultrasound abnormalities in small for gestational age or growth-restricted infants born over 32 weeks gestation: A systematic review and meta-analysis. *Brain Sciences*, *12*, 1713. https://doi.org/10.3390/brainsci12121713

Rushe, T.M., Temple, C.M., Rifkin, L., Woodruff, P.W.R., Bullmore, E.T., Stewart, A.L., Simmons, A., Russell, T.A., & Murray, R.M. (2004). Lateralisation of language function in young adults born very preterm. *Archives of Disease in Childhood: Fetal and Neonatal Edition, 89*, 112-118. https://doi.org/10.1136/adc.2001.005314

Rvachew, S., Royle, P., Gonnerman, L.M., Stank, B., Marquis, A., & Herbay, A. (2017). Development of a tool to screen risk of literacy delays in French-speaking children: PHOPHLO. *Canadian Journal of Speech-Language Pathology and Audiology*, 41(3), 321-340.

Salat, D.H. (2014). Diffusion tensor imaging in the study of aging and age-associated neural disease. In H. Johansen-B., & T.E.J. Behrens, *Diffusion MRI* (2nd edition, pp. 257-281). Academic Press. https://doi.org/10.1016/B978-0-12-396460-1.00012-3

Sanchez, K., Spittle, A.J., Cheong, J.L.Y., Thompson, D.K., Doyle, L.W., Anderson, P.J., & Morgan, A.T. (2019). Language in 2-year-old children born preterm and term: a cohort study. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, *104*, 647-652. https://doi.org/10.1136/archdischild-2018-315843

Sansavini, A., Zuccarini, M., Gibertoni, D., Bello, A., Caselli, M.C., Corvaglia, L., & Guarini, A. (2021). Language profiles and their relation to cognitive and motor skills at 30 months of age: An online investigation of low-risk preterm and full-term children. *Journal of Speech, Language and Hearing Research, 64*, 2715-2733. https://doi.org/10.1044/2021_JSLHR-20-00636

Schaefer, P.W., Grant, P.E., & Gonzalez, R.G. (2000). Diffusion-weighted MR imaging of the brain. *Radiology*, *217*, 331-345.

Schardt, C., Adams, M.B., Owens, T., Keitz, S., & Fontelo, P. (2007). Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Medical Informatics and Decision Making*, *7*(16). https://doi.org/10.1186/1472-6947-7-16

[3] Schmidbauer, V.U., Yildirim, M.S., Dovjak, G.O., Goeral, K., Buchmayer, J., Weber, M., Kienast, P., Diogo, MC., Prayer, F., Stuempflen, M., Kinttinger, J., Malik, J., Nowak, N.M., Klebermass-Schrehof, K., Fuiko, R., Berger, A., Prayer, D., Kasparian, G., & Giordano, V. (2024). Quantitative Magnetic Resonance Imaging for neurodevelopmental outcome prediction in neonates born extremely premature – An exploratory study. *Clinical Neuroradiology*, *34*, 421-429. https://doi.org/10.1007/s00062-023-01378-9

Scott, J.A., Habas, P.A., Kim, K., Rajagopalan, V., Hamzelou, K.S., Corbett-Detig, J.M., Barkovich, A.J., Glenn, O.A., & Studholme, C. (2011). Growth trajectories of the human fetal brain tissues estimated from 3D reconstructed *in utero* MRI. *International Journal of Developmental Neuroscience*, *29*(5), 529-536. https://doi.org/10.1016/j.ijdevneu.2011.04.001

Scott Tomlinson, M., Santos, H.P., Stewart, J.R., Joseph, R., Leviton, A., Onderdonk, A.B., Kuban, K.C.K., Heeren, T., O'Shea, T.M., & Fry, R.C. (2020). Neurocognitive and social-communicative function of children born very preterm at 10 years of age: Associations with microorganisms recovered from placenta parenchyma. *Journal of Perinatology, 40*, 306-315. https://doi.org/10.1038/s41372-019-0505-8

Scratch, S.E., Anderson, P.J., Doyle, L.W., Thompson, D.K., Ahmadzai, Z.M., Greaves, R.F., Inder, T.E., & Hunt, R.W. (2015). High postnatal growth hormone levels are related to cognitive deficits in a group of children born very preterm. *The Journal of Clinical Endocrinology and Metabolism*, *100*(7), 2709-2717. https://doi.org/10.1016/j.jpeds.2007.06.043

Seaton, S.E., Agarwal, R., Draper, E.S., Fenton, A.C., Kurinczuk, J.J., Manktelow, B.N., & Smith, L.K. (2023). Estimated neonatal survival of very preterm births across the care pathway: a UK cohort 2016–2020. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, *108*, 562-568. https://doi.org/10.1136/archdischild-2022-324987

Shah, P.S., Lui, K., Sjörs, G., Mirea, L., Reichman, B., Adams, M., Modi, N., Darlow, B.A., Kusuda, S., San Feliciano, L., Yang, J., Hakansson, S., Mori, R., Bassler, D., Figueras-Aloy, J., & Lee, S.K. (2016). *Journal of Pediatrics, 177*, 144-152. https://doi.org/10.1016/j.jpeds.2016.04.083

Sheng, M., Guo, T., Mabbott, C., Chau, V., Synnes, A., De Vries, L.S., Grunau, R.E., & Miller, S.P. (2022). Ventricular volume in infants born very preterm: relationship with brain maturation and neurodevelopment at age 4.5 years. *Journal of Pediatrics*, *248*, 251-258. https://doi.org/10.1016/j.jpeds.2022.05.003

[23] Skiöld, B., Alexandrou, A., Padilla, N., Blennow, M., Vollmer, B., & Ådén, U. (2014). Sex differences in outcome and associations with neonatal brain morphology in extremely preterm children. *Journal of Pediatrics*, *164*(5), 1012-1018. https://doi.org/10.1016/j.jpeds.2013.12.051

[26] Skiöld, B., Vollmer, B., Böhm, B., Hallberg, B., Horsch, S., Mosskin, M., Lagercrantz, H., Ådén, U., & Blennow, M. (2012). Neonatal magnetic resonance imaging and outcome at age 30 months in extremely preterm infants. *Journal of Pediatrics*, *160*(4), 559-566. https://doi.org/10.1016/j.jpeds.2011.09.053

Smith, L.K., Draper, E.S., Manktelow, B.N., & Field, D.J. (2009). Socioeconomic inequalities in survival and provision of neonatal care: population based study of very preterm infants. *Britsh Medical Journal*, 339:b4702. https://doi.org/10.1136/bmj.b4702

Song, I.G. (2023). Neurodevelopmental outcomes of preterm infants. *Clinical and Experimental Pediatrics*, *66*(7), 281-287. http://doi.org/10.1016/j.vaccine.2016.03.045

Soria-Pastor, S., Padilla, N., Zubiaurre-Elorza, L., Ibarretxe-Bilbao, N., Botet, F., Costas-Moragas, C., Falcon, C., Bargallo, N., Mercader, J.M., & Junqué, C. (2007). *Pediatrics*, *124*(6), 1161-1170. https://doi.org/10.1542/peds.2009-0244

Stipdonk, L.W., Dudink, J., Utens, E.M.W.J., Reis, I.K., Franken, M-C.J.P. (2020). Language functions deserve more attention in follow-up of children born very preterm. *European Pediatric Neurology Society*, *26*, 75-81. https://doi.org/10.1016/j.ejpn.2020.02.004

Stipdonk, L.W., Franken, M-C.J.P., & Dudink, J. (2018). Language outcome related to brain structures in school-aged preterm children: A systematic review. *PLoS ONE*, *13*(6), e0196607. https://doi.org/10.1371/journal.pone.0196607

Story, L., Davidson, A., Patkee, P., Fleiss, B., Kyriakopoulou, V., Colford, K., Sankaranf, S., Seeda, P., Jones, A., Hutter, J., Shennan, A., & Rutherford, M. (2021). Brain volumetry in fetuses that deliver very preterm: An MRI pilot study. *NeuroImage: Clinical*, *30*, 102650. https://doi.org/10.1016/j.nicl.2021.102650

Symms, M., Jäger, H.R., Schmierer, K., & Yousry, T.A. (2004). A review of structural magnetic resonance neuroimaging. *Journal of Neurology, Neurosurgery and Psychiatry*, *75*, 1235-1244. https://doi.org/10.1136/jnnp.2003.032714

Thompson, D.K., Matthews, L.G., Alexander, B., Lee, K.J., Kelly, C.E., Adamson, C.L., Hunt, R.W., Cheong, J.L.Y, Spencer-Smith, M., Neil, J.J., Seal, M.L., Inder, T.E., Doyle, L.W., & Anderson, P.J. (2020). Tracking regional brain growth up to age 13 in children born term and very preterm. *Nature Communications*, *11*, 696-696. https://doi.org/10.1038/s41467-020-14334-9

Torres-González, C., Ricardo-Garcell, J., Alvarez-Núñez, D., & Galindo-Aldana, G. (2024). Intellectual development in Mexican preterm children at risk of perinatal brain damage: A longitudinal study. *Children*, *11*(6), 652. https://doi.org/.3390/children11060652

[4] Trimarco, E., Jafrasteh, B., Jiménez-Luque, N., Almagro, Y.M., Ruiz, M.R., Gutiérrez, M.L., González, E.R., Arenas, A.S., Lubián-López, S.M., & Bernavente-Fernández, I. (2024). Thalamic volume in very preterm infants: associations with severe brain injury and neurodevelopmental outcome at two years. *Frontiers in Neurology*, *1*5, 142273. https://doi.org./10.3389/fneur.2024.1427273

Vandormael, C. Schoenhals, L., Hüppi, P. S., Filippa, M., & Tosla, C.B. (2019). Language in preterm born children: Atypical development and effects of early interventions on neuroplasticity. *Neural Plasticity, 2019*, 1-10. https://doi.org/10.1155/2019/6873270

Van Noort-Van der Spek, I. L., Franken, M. J. P., & Kuperus-Weisglas, N. (2012). Language functions in preterm-born children: A systematic review and meta-analysis. *Pediatrics, 129*(4), 745-754. https://doi.org/10.1542/peds.2011-1728

Varela-Moraga, V., Arce-Montero, C., Osorio-Saldaña, Ramirez-Carreño, F., & Quezada-Gaponov, C. (2023). Vocabulary size in very preterm and extremely preterm infants: A cross-sectional study. *Revista Chilena de Fonoaudiología 22*(1), 1-11. https://doi.org/10.5354/0719-4692.2023.66681

[15] Vassar, R., Schadl, K., Cahill-Rowley, K., Yeom, K., Stevenson, D., & Rose, J. (2020). Neonatal brain microstructure and machine-learning-based prediction of early language development in children born very preterm. *Pediatric Neurology*, *108,* 86e92. https://doi.org/10.1016/j.pediatrneurol.2020.02.007

Visu-Petra, L., Cheie, L., Benga, O., & Miclea, M. (2012). The structure of executive functions in preschoolers: An investigation using the NEPSY battery. *Precedia – Social and Behavioral Sciences*, *33*, 627-631. https://doi.org/ 10.1016/j.sbspro.2012.01.197

Vohr, B. (2014). Speech and language outcomes of very preterm infants. *Seminars in Fetal & Neonatal Medicine*, *19*, 78e83. https://doi.org/10.1016/j.siny.2013.10.007

[6] Wang, X., Trabatti, C., Weeke, L., Dudink, J., Swanenburg de Vreye, H., Eijsermans, R.M.J.C., Koopman-Esseboom, C., Benders, M.J.N.L., & Tataranno M.L. (2023). Early qualitative and quantitative amplitude-integrated electroencephalogram and raw electroencephalogram for predicting long-term neurodevelopmental outcomes in extremely preterm infants in the Netherlands: A 10-year cohort study. *Lancet Digital Health*, *5*, 895-904. https://doi.org/10.1016/S2589-7500(23)00198-X

Wehrle, F.M., Michels, L., Guggenbergerf, R., Hubera, R., Latala, B., O'Gormance, R.L., & Hagmann, C.F. (2018). Altered resting-state functional connectivity in children and adolescents born very preterm short title. *NeuroImage Clinical, 20*, 1148-1156. https://doi.org/10.1016/j.nicl.2018.10.002

Wierenga, L., Langen, M., Ambrosino, S., Van Dijk, S., Oranje, B., & Durston, S. (2014). Typical development of basal ganglia, hippocampus, amygdala and cerebellum from age 7 to 24. *NeuroImage*, *96*, 67-72. https://doi.org/ 10.1016/j.neuroimage.2014.03.072

[27] Woodward, L.J., Clark, C.A.C., Bora, S., & Inder, T.E. (2012). Neonatal white matter abnormalities an important predictor of neurocognitive outcome for very preterm children. *PLoS ONE*, *7*(12), e51879. https://doi.org/10.1371/journal.pone.0051879

World Health Organization. (2023, 10 May). *Preterm birth*. https://www.who.int/news-room/fact-sheets/detail/preterm-birth

Young, S., Murray, K., Mwesigwa, J., Natureeba, P., Osterbauer, B., Achan, J., Arinaitwe, E., Clark, T., Ades, V., Plenty, A., Charlebois, E., Tuel, T., Kamya, M., Havlir, D., & Cohan, D. (2012). Maternal nutritional status predicts adverse birth outcomes among HIV-infected rural Ugandan women receiving combination antiretroviral therapy. *PLoS ONE*, *7*(8), e41934. https://doi.org/10.1371/journal.pone.0041934

[22] Young, J.M., Powell, T.L., Morgan, B.R., Card, D., Lee, W., Smith, M.L., Sled, J.G., & Taylor, M.J. (2015). Deep grey matter growth predicts neurodevelopmental outcomes in very preterm children. *NeuroImage*, *11*, 360-368. https://doi.org/10.1016/j.neuroimage.2015.02.030

Zimmerman, E. (2018). Do infants born very premature and who have very low birth weight catch up with their full term peers in their language abilities by early school age? *Journal of Speech, Language and Hearing Research*, *61*, 53-65. https://doi.org/10.1044/2017_JSLHR-L-16-0150

Disclosure Statement Generative AI

In this writing assignment, I utilized generative AI, specifically Gemini version 1.5, in the final writing phase of the literature review. The generative AI tool was used as an additional grammar checker (for some paragraphs). I have critically examined all suggestions and improvements that were given by Gemini. This usage was completely in accordance with the guidelines of the GSLS for generative AI (https://students.uu.nl/en/gsls/practical-information/generative-ai-guidelines).

Open AI. (2024). *Gemini* (Nov 7 version) [Large language model]. https://gemini.google.com/app

Appendix

		Brain Morphometry	Brain Volumes	WM Microstructure & Connectivity	Structural Abnormalities	Miscellaneous Predictors
Oral Language	**Expressive & Receptive Language**	*CT* + frontal lobe [5] *GI* 0 [5] *ICC* + L insula [13] + L STG [13] *SA* - frontal lobe [5] + L parietal lobe [13] *SD* + frontal lobe [5] - occipital lobe [5]	***CL*** 0 caudate [22] + CB [16] - CSF [5] ↑[8]; - [14; 24] DWMA - CSO [24] - PV [24] 0 GB [22] 0 GP [22] + putamen [22] + [4]; 0 [22] thalamus + WM [21] ***EL*** 0 CB [16] ***RL*** + CB [16] + CGM [21] + DGM [21] + WM [21]	***WM connectivity*** ↑ [8] 0 [18] ***WM microstructure*** ***CL*** *AD* + L cingulum [9] ↑ R lingual gyrus [15] *FA* 0 [9; 10; 18; 19] - CC-OCC [11] + L ILF [11] 0 R ILF [11] 0 L/R UF [11] *MD* 0 [10; 11] ↑ R sagittal stratum [15] ↑ R IOG [15] ***EL*** *AD* ↑ R sagittal stratum [15] *FA* ↑ L STG [15] *MD* ↑ R ITG [15] ***RL*** *AD* ↑ R PLIC [15] ↑ R SPG [15] *MD* ↑ L SFG [15]	***CL*** *WM* 0 [14; 15] - CA [27] - SAB [27] - CC thinning [27] 0 VD [27] - volume [27] ***RL*** *CB* - [15]	*rsfMRI* ↑ [8] *VBI* - [2]
	Grammar		+ WM [21]		*WM* 0 [25]	
	Semantics		+ CGM [21] + WM [21]		*WM* 0 [25]	
	Pragmatics				*WM* 0 [25]	
PA					*WM* - [25]	
VF	**Phonemic VF**				*CUS* 0 [28]	
	Semantic VF				*CUS* 0 [28]	

Written Language	**Reading**				*CB* 0 [**12**; **17**] *CGM* 0 [**17**] *CUS* 0 [**28**] *DGM* - [**17**] *GB* 0 [**17**] *WM* 0 [**12**; **17**]	
	Spelling				*CB* 0 [**12**; **17**] *CGM* 0 [**17**] *CUS* 0 [**28**] *DGM* - [**17**] *GB* - [**17**] *WM* 0 [**12**; **17**]	

Table A1. *Overview of the study results on the correlation between neuroimaging biomarkers and language outcomes in VPT children*

Note: AD = axial diffusivity; CA = cystic abnormalities; CB = cerebellum; CC = corpus callosum; CC-OCC = corpus callosum occipital segment; CGM = cortical gray matter; CL = core language (language composite score); CSF = cerebrospinal fluid; CSO = centrum semi-ovale; CT = cortical thickness; CUS = cranial ultrasound; DGM = deep gray matter; DWMA = diffuse white matter abnormalities; EL = expressive language; FA = fractional anisotropy; GB = global brain; GI = gyrification index; GP = globus pallidus; ICC = inner cortical curvature; ILF = inferior longitudinal fasciculus; IOG = inferior occipital gyrus; ITG = inferior temporal gyrus; L = left; MD = mean diffusivity; PA = phonological awareness; PLIC = posterior limb of internal capsule; PV = periventricular region; R = right; RL = receptive language; rsfMRI = resting-state functional magnetic resonance imaging; SA = surface area; SAB = signal abnormality; SD = sulcal depth; SFG = superior frontal gyrus; SPG = superior parietal gyrus; STG = superior temporal gyrus; UF = uncinate fasciculus; VBI = ventricle-to-brain index; VD = ventricular dilatation; VF = verbal fluency; WM = white matter

'-' indicates a significant negative correlation; '+' indicates a significant positive correlation; '0' indicates an insignificant correlation; '↑' indicates high (significant) classification accuracy; '↓' indicates low (insignificant) classification accuracy

NB: empty cells indicate that no study has tested the correlation between that language subdomain and biomarker yet.

		Brain Morphometry	Brain Volumes	WM Microstructure & Connectivity	Structural Abnormalities	Miscellaneous Predictors
Oral Language	**Expressive & Receptive Language**	***EL*** *SSA* - L IFS [20] *SD* + L LF [20] ***RL*** *SSA* - L IFS [20] + L LF [20] *SD* + L LF [20] *SI* - L IFS [20] + L LF [20]	***CL*** + CGM [23] + cingulate [23] ***EL*** + brain stem [23] + DGM [23] + WM [23] + precuneus [23]	***WM connectivity*** - cerebellum [1] - CSPT & CSTT [1] - middle CB peduncles [1] - posterior commissure [1] ***WM microstructure*** *ADC* 0 [23] 0 L/R PLIC [3] 0 midbrain [3] 0 medulla oblongata [3] 0 pontine tegmentum [3] *FA* 0 [23] 0 L/R PLIC [3] 0 midbrain [3] 0 medulla oblongata [3] 0 pontine tegmentum [3]	*CB* ∅ [7] *CGM* ⇑ [7] *DPB* ∅ [7] *IHD* ∅ [7] *TCD* ∅ [7] *VD* ∅ [7] *WM* ∅ [7] - [26]	*(a)EEG* ↑ [6] *T1/T2 RT* 0 L/R PLIC [3] 0 midbrain [3] 0 medulla oblongata [3] 0 pontine tegmentum [3]

Table A2. *Overview of the study results on the correlation between neuroimaging biomarkers and language outcomes in EPT children*

Note: ADC = apparent diffusion coefficient; (a)EEG = (amplitude-integrated) electroencephalography; CB = cerebellum; CGM = cortical gray matter; CL = core language (language composite score); CSPT = corticospinal tract; CSTT = corticostriatal tract; DBP = diameter biparietal; DGM = deep gray matter; EL = expressive language; FA = fractional anisotropy; IFS = inferior frontal sulcus; IHD = interhemispheric distance; L = left; LF = lateral fissure; PLIC = posterior limb of internal capsule; R = right; RL = receptive language; RT = relaxation times; SSA = sulcal surface area; SD = sulcal depth; SI = sulcal index; TCD = trans-cerebellar distance; VD = ventricular dilatation; WM = white matter

'-' indicates a significant negative correlation; '+' indicates a significant positive correlation; '0' indicates an insignificant correlation; '↑' indicates high (significant) classification accuracy; '↓' indicates low (insignificant) classification accuracy; '⇑' indicates significant odds ratio; '∅' indicates insignificant odds ratio