Executive Function and its Impact on Academic and Behavior Problems in Very Preterm Children

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Executieve functies en hun effect op de schoolprestaties en
het gedrag van zeer vroeg geboren kinderen

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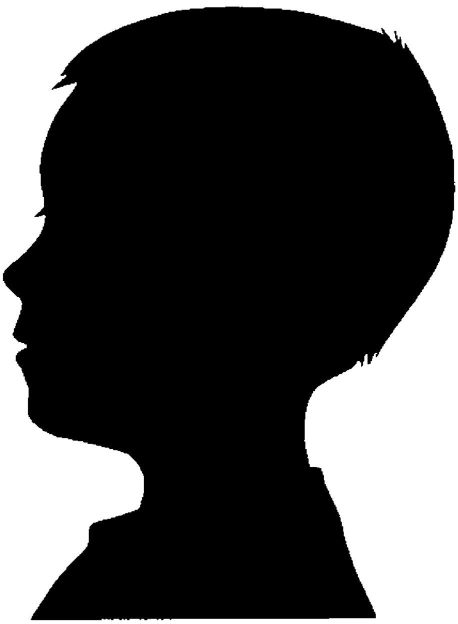
General Introduction



INTRODUCTION

Preterm birth occurs before 37 weeks of gestation and includes late preterm birth (gestational age: 32-37 weeks), very preterm birth (gestational age < 32 weeks), and extremely preterm birth (gestational age < 27 weeks) according to the World Health Organization (2010).[1] Risk factors associated with preterm birth include ethnicity, multiple pregnancies, pregnancy after in vitro fertilization, maternal or infant infections, and unfavorable social environmental circumstances.[2] The obstetric precursors leading to preterm birth are delivery for maternal or fetal indications, in which labor is either induced or the infant is delivered by caesarean section, spontaneous preterm labor with intact membranes, and, preterm premature rupture of the membranes, irrespective of whether delivery is vaginal or by caesarean section.[2] In the Netherlands, 7.7% of all births are preterm and 1.5% are very preterm.[3] Because of technological advances and collaboration between obstetricians and neonatologists, survival rates for (very) preterm infants have dramatically increased. A 1-kg infant who was born in 1960 had a mortality risk of 95% but had a 95% probability of survival by 2000.[4]

Despite the improved perinatal care, developmental outcomes of these infants remain of concern since immature organs, such as brains and lungs, are extremely vulnerable for adverse consequences of very preterm birth.[5] Adverse developmental outcomes include respiratory illnesses and abnormal growth patterns, but also severe neurosensory disabilities, such as cerebral palsy, mental retardation, and deafness or blindness.[5-6] These problems are generally detected and treated early in infancy and the incidence is fortunately relatively low.[6-7] There is growing awareness, however, that the majority of very preterm children that survive without such overt neurosensory disabilities and with normal intelligence suffers from long-term problems. These long-term problems become apparent at school age and comprise fine and gross motor dysfunction,[8] neurocognitive dysfunction such as impaired visuo-spatial, or language skills,[6] poor academic achievement, and behavior problems.[9] In the Netherlands, 38% of these children have special assistance at school[10] and about 20% attend special education[10] compared to 4.8% of the normal population.

Academic achievement and behavioral functioning are important markers of whether a child can keep up with same aged peers and enter into social relationships and have extensively been evaluated in very preterm children. Poor academic achievement in this population includes severe deficits in mathematics, reading, and spelling (**Chapters 2 and 3**),[9] and in preschool the lack of mastery of pre-academic skills, such as numerical reasoning skills (**Chapter 3**).[11] Behavior problems that are most prominent are symptoms of inattention and internalizing behavioral problems (**Chapter 2**).[9]

Comparable to the hurdle of severe disabilities early in infancy for development, so does the lack of appropriate academic and behavioral skills hinder functioning when the environment becomes more complex and demanding in preschool and beyond. This long-term morbidity following very preterm birth extends to adult life which places a great burden on families as well as health and educational services, and results in enormous economic costs.[12] Efforts to improve understanding and early identification of the academic and behavior problems following very preterm birth in order to help these children overcome these adverse outcomes are needed.

Executive function (EF) has been considered one of the crucial mechanisms underlying academic and behavioral problems in term children.[13-20] EF refers to interrelated neuro-cognitive processes, which are essential for a child's appropriate academic, behavioral and social functioning.[21-22] Factor analyses have demonstrated that the concept EF is characterized by a fractionated ability structure including the key processes inhibitory control (i.e. suppression of responses to irrelevant stimuli), working memory (i.e. capacity to mentally manipulate information in mind), switching, also referred to as shifting or cognitive flexibility (i.e. alternation between mental sets/strategies), planning (i.e. development of strategies to reach a future goal), and fluency (i.e. generating as many different solutions for a particular problem as possible).[23-25] EF is not entirely mature before young adulthood,[26] although research has shown that executive processes exist and are functional yet in early childhood.[27-28] EF is important in novel situations and enables to respond to unexpected stimuli.[21] Poor EF may thus cause a lack of requisites for functioning in a complex and demanding environment. It has been shown to rely strongly on prefrontal cortex functioning and white matter connections with striatal and thalamic regions.[29-31] Development of measures suitable to assess these rudimentary forms of EF in young children has accelerated,[32] which stimulated research to examine development of EF in clinical groups.

Given that EFs are 'higher-order' functions which integrate input and output of various 'lower-order' modalities[33-34] they are highly dependent on the quality and capacity of neural networks (e.g. thalamocortical and striatalcortical pathways) across the brain.[35-37] Damage to one or more of these components may substantially affect EF in very preterm children. Because of the unique cerebrovascular anatomy and physiology,[38] immature brains of very preterm babies are highly vulnerable for damage in the abnormal milieu of extrauterine life. For example, the blood-brain barrier does not function efficiently at 27 weeks of gestational age due to immaturity of endothelial and ependymal cells which allows toxins to enter the infant's brain. The quality and capacity of the neural networks may be severely injured in children with periventricular leukomalacia.[39] There is, however, growing awareness that also the very preterm child without such overt focal brain lesions may have subtle white and gray matter structure damage.[40] The most common detected type of injury now is diffuse cerebral white matter.[38] This injury in turn may lead to delayed or impaired myelinisation, altered dendritic connectivity, and deviations in cortical gray matter volumes.[40-43] Both abnormal reductions as well as excesses in white and gray matter volumes have been observed;[44] alterations tend to also persist over time.[45-46] Recent studies provide evidence that diffuse white matter structure damage in combination with abnormal gray matter volumes affect the quality of the thalamocortical and striatalcortical connections[47] which in turn is linearly related to impaired EF in very preterm children, accounting for up to 29% of the variance in EF.[44,48-56]

Because affected EF may be a possible explanatory mechanism underlying the scholastic, adaptive, and behavioral difficulties in very preterm children,[13-17,24] the amount of research on EF in this population has increased substantially the last decade. Studies have consistently described that EF is impaired in very preterm children.[9,57] However, a great diversity exists between studies, with respect to which executive skills are particularly found to be affected and whether the found EF impairments in fact reflect information processing deficiencies. It has also been questioned to what extent EF impairments persist over time in this population. Reasons for this diversity include among others a focus on isolated aspects of EF in the different studies instead of on a broader array of EFs. Other reasons of the diversity found in the studies are comparison of very preterm children's performance to that of small control samples, divergence between studies in children's age at assessment, diversity in measures to assess EF, employment of measures that rely heavily on 'lower-order' processes such as motor coordination or processing speed, and employment of measures that tap into multiple aspects of EF. Well-established EFs of importance for academic and behavioral functioning, such as inhibitory control and interference control, which have been considered to be the underlying symptoms of inattention,[19,58] have only scarcely been assessed in very preterm children.[9,57] Our current understanding of neonatal and social environmental factors associated with impaired EF in very preterm children is limited. A number of earlier studies found evidence that a higher degree of neonatal illness is significantly associated with poorer EF,[59] albeit other studies failed to confirm these findings. In addition, some studies employed composite measures of neonatal illness[59-61] leaving unclear which neonatal risk variable was exactly related to impaired EF in very preterm children. Furthermore, effects of age have not been examined, although possibly probable relationships between these factors may vary with age. Neonatal or biomedical factors may, for instance, be more influential in early development, whereas parental education may become more important as children grow older.

Contrasting to the increasing body of literature on group differences in EF between very preterm and term children, studies linking EF to academic achievement and behavioral difficulties in the very preterm group are scarce.[62-66] Available studies have shown that very preterm children's poor inhibitory control and working memory skills are related to academic underperformance and inattentive behavior. Some studies, however, suggested that this link was fully accounted for by slow processing speed,[62,67] whereas another study found a cascade of effects with slow processing speed being related to poor EF, that in turn was related to lower achievement in mathematics and reading.[66] These confusing results call for further disentanglement of the exact contribution of EF versus information processing indices to academic and behavior problems in very preterm children. A restriction of earlier studies is the absence of use of control groups or the use of small control groups, which limited their possibility to calculate whether the effects of EF on outcome measures differed between children born very preterm and at term. In addition, earlier studies have included very preterm children at middle school age leaving unclear as to whether links between EF and school outcomes are already apparent at early school ages. Thus, although earlier findings are promising, the evidence that poor EF underpins academic and behavior difficulties in very preterm children is based on very few studies and leaves a number of issues unclear. This impedes on the study of efficacy and feasibility of tailored intervention programs to remediate EF in children.

Aims of this thesis project are to provide a detailed picture of EF in very preterm children of 4.0 to 12.0 years of age and to investigate the predictive role of neonatal and social environmental factors for impaired EF. Having unraveled the currently existing inconsistencies and unclearness on these issues, the project will move on and study the impact of impaired EF on poor academic achievement and behavior problems related to very preterm birth.

Three research questions are guiding:

1. What is the profile of strengths and weaknesses in EF in very preterm children and to what extend does this profile persist from preschool to the end of primary schooling?
2. What neonatal and social environmental factors are predictive for impaired EF in very preterm children?
3. What is the impact of impaired EF on academic achievement and behavior in very preterm children?

The first research question will be answered in **Chapters 4 and 5**. **Chapter 4** reports on a study that assessed a comprehensive range of EF domains very preterm children aged 4.0 to 12.0 years. Domains assessed were those identified by factor analytic studies into the structure of EF in children and included inhibitory control, working memory, cognitive flexibility, verbal fluency, and planning.[25-26,68-69] Measures employed were suitable for children in preschool as well as in primary school (i.e. 4.0 to 12.0 years) in order to examine stability of executive deficits over time. **Chapter 5** reports on a study that assessed a comprehensive range of EF in very preterm children at early school age, including the domains inhibitory control, working memory, switching, verbal fluency, and conceptual reasoning. Measures employed in this study were specifically developed and suitable for children at preschool ages. A second characteristic of these measures was that a majority had baseline control conditions with similar stimuli but without an EF load, to isolate impaired EF processes from impaired 'lower-order' processes.

Both the study reported in **Chapter 4** as well as the study reported in **Chapter 5** examined whether EF in very preterm children depends on processing speed. Measures employed required computerized or verbal responding which would not appeal to fine-motor skills which have been found to be impaired in very preterm children.[8] The two studies also addressed whether poor EF in very preterm children can be distinguished from low IQ scores.

The second research question will be answered in **Chapters 5 and 6**. In **Chapter 5**, a composite score of neonatal risk was regressed on EF test scores of very preterm children. This composite score was calculated with the neurobiological risk score (NBRS)[70] that summarizes neonatal medical events, with higher scores indicating higher degree of neurobiological risk. **Chapter 6** examined a range of neonatal risk factors that are selected on the basis of the most common neonatal risk factors of adverse outcomes identified in the literature including gestational age, birth weight standard deviation score, postnatal growth at 6 weeks corrected age, intra ventricular hemorrhage grade III and IV, oxygen dependency at 36 weeks postconceptional age, and the incidence of meningitis and necrotizing enterocolitis. Parental education served as an index for social environmental circumstances, since this is an important predictor for child development in term[71] as well as in very preterm children.[72] Neonatal risk factors as well as parental education are retrospectively collected.

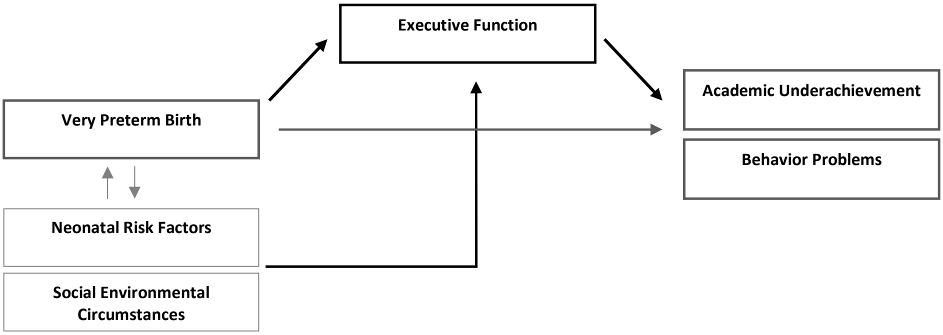
The third research question will be answered in **Chapter 7**. This chapter reports on a study in which the impact of EF on poor mathematical achievement and attention problems is examined. Poor mathematical achievement and attention problems are chosen as outcome parameters since these are two most pronounced adverse outcomes in very preterm children.[9,11] Mathematical achievement assessed with the Dutch National Pupil Monitoring System.[73] Attentional functioning is assessed using the standardized questionnaires Child Behavior Checklist (CBCL/1-5 or CBCL/6-18),[74-75] Teacher Report

Form (TRF/1-5 or TRF/6-18),[74-75] and Disruptive Behavior Disorders Rating scale.[76-77] Contrasting to earlier studies on this subject, we calculated the unique contribution of EF for mathematics and attentional functioning over and above that of processing speed indices and IQ.

Two different samples of very preterm children have been examined in the above described studies. The first sample consisted of 200 very preterm children (gestational age ≤ 30 weeks) aged 4.0 to 12.0 years, with approximately 30 children in each year group (e.g. 4.0 to 4.9 years), to ensure a power of > 0.88. This sample was obtained from all (n = 706) very preterm surviving singletons admitted between 1996-2004 to the neonatal intensive care unit (NICU) of the Erasmus University Medical Center-Sophia Children's Hospital Rotterdam, The Netherlands. There were no differences with respect to gestational age, birthweight, and duration of NICU-stay, between the included year cohorts (each year cohort was compared with all other year cohorts, all Fs < 0.8; all ps > 0.6). Data of the very preterm sample were compared to that of a term control group comparable in age and gender. The term children were recruited from three regular primary schools located in the same neighborhoods as the schools attended by the very preterm children. Parents of all children attending these three schools were invited to participate by letter. All parents that gave permission for their child to participate signed an informed consent and gave information on perinatal characteristics, neurological functioning, and presence of minor disabilities in their term born children. Only children without histories of prematurity (gestational age > 37 weeks), perinatal complications, neurological disorders, were included in the control group. Exclusion criteria for both groups were multiple births and mental and/or motor handicaps too profound to allow task execution.

The second sample consisting of 50 children born very preterm (gestational age ≤ 30 weeks) was, consecutively and randomly, acquired from the total population of very preterm survivors (n = 276) born and had been admitted between 1998-1999 to the neonatal intensive care unit (NICU) of the Erasmus University Medical Center-Sophia Children's Hospital Rotterdam, The Netherlands. Data of the very preterm children were compared to that of a term control group (mean gestational age = 39.7, SD = 1.3; mean birthweight = 3579, SD = 510) who were recruited from local elementary schools as a part of a normative study of the VU University Amsterdam. Included in the control group were normally developing children without histories of prematurity (gestational age > 37 weeks), perinatal complications, psychiatric and neurological disorders. Exclusion criteria for both groups were multiple births and mental and/or motor handicaps too profound to allow task execution.

FIGURE 1 Project Design



Grey lines refer to what is known. **Black lines** refer to what this project adds.

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Chapter 2

Meta-analysis of neurobehavioral outcomes in very preterm and/or VLBW children

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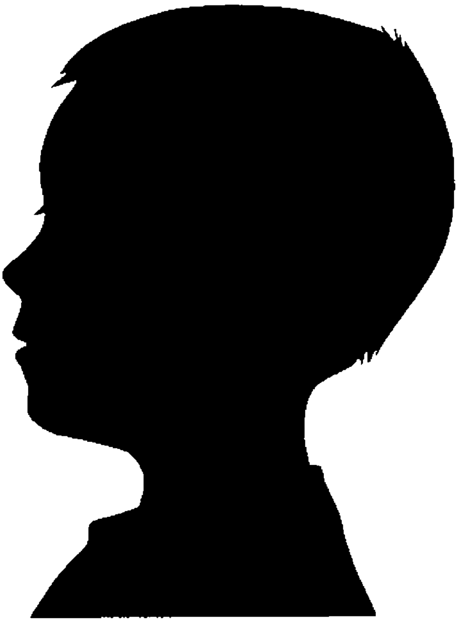

ABSTRACT

Objective

Sequelae of academic underachievement, behavioral problems and poor executive function (EF) have been extensively reported for very preterm (gestational age ≤ 33 weeks) and/or very low birth weight (VLBW ≤ 1500 g) children. Great variability in the published results, however, hinders the field to study underlying dysfunctions and develop intervention strategies. We conducted a quantitative meta-analysis of studies published between 1998 and 2008 on academic achievement, behavioral functioning and EF with the aim of providing aggregated measures of effect size for these outcome domains.

Methods

Suitable for inclusion were 14 studies on academic achievement, 9 studies on behavioral problems, and 12 studies on EF, which compared a total of 4125 very preterm and/or VLBW children with 3197 term-born controls. Combined effect sizes for the 3 outcome domains were calculated in terms of Cohen's *d*. *Q*-test statistics were performed to test homogeneity among the obtained effect sizes. Pearson's correlation coefficients were calculated to examine the impact of mean birth weight and mean gestational age, as well as the influence of mean age at assessment on the effect sizes for academic achievement, behavioral problems, and EF.

Results

Combined effect sizes show that very preterm and/or VLBW children score .60 SD lower on mathematics tests, 0.48 SD on reading tests and 0.76 SD on spelling tests than term born peers. Of all behavioral problems stacked, attention problems were most pronounced in very preterm and/or VLBW children with teacher and parent ratings being 0.43 SD to 0.59 SD higher than for controls, respectively. Combined effect sizes for parents and teacher ratings of internalizing behavior problems were small ($p < 0.28$) and for externalizing behavior problems negligible ($p < 0.09$) and not significant. Combined effect sizes for EF revealed a decrement of 0.57 SD for verbal fluency, 0.36 SD for working memory, and 0.49 SD for cognitive flexibility in comparison to controls. Mean age at assessment was not correlated with the strength of the effect sizes. Mathematics and reading performance, parent ratings of internalizing problems, teacher ratings of externalizing behavior and attention problems, showed strong and positive correlations with mean birthweight and mean gestational age (all $r_s > 0.51$).

Conclusions

Very preterm and/or VLBW children have moderate to severe deficits in academic achievement, attention problems, internalizing behavioral problems and poor EF; adverse outcomes that were strongly correlated to their immaturity at birth. During transition to young adulthood these children continue to lag behind their term born peers.

INTRODUCTION

Improvements in perinatal care have resulted in increased survival rates for children born very preterm (gestational age ≤ 33 weeks) and/or with a very low birth weight (VLBW ≤ 1500 g). The incidence of major disabilities, such as cerebral palsy, mental retardation, deafness or blindness is fairly low.[1] There is growing awareness that the majority of non-disabled survivors encounter more "subtle" problems, such as academic underachievement,[2] behavioral problems,[3-5] and deficits in higher-order neurocognitive functions: the so-called executive functions (EF),[6] which persist throughout childhood and young adulthood.[1,4,7] However, great variability exists in the published results due to small numbers of participants, high attrition rates, and substantial variations in methods and study design. We conducted a quantitative meta-analysis to integrate prior research on academic achievement, behavioral problems and EF in very preterm, and/or VLBW children, in order to provide aggregated measures of effect sizes for these three outcome domains. Such an aggregation will facilitate the field to move forward to study underlying dysfunctions and develop intervention strategies.

Academic achievement includes mathematics, reading, and spelling, of which the literature suggests that the poorest performance of very preterm and/or VLBW children is observed in mathematics[2]. Behavioral problems in these children mainly manifest in an increased risk for Attention Deficit/Hyperactivity Disorder (AD/HD)[3] and internalizing behavioral problems, such as withdrawn behavior,[6] though some studies have also found oppositional behavior.[8,9] A large body of evidence has shown that academic underachievement and behavioral problems arise from a deficit in EF,[10-13] a set of neurocognitive functions, such as inhibitory control, working memory, cognitive flexibility, and planning.[14] EF has therefore attracted considerable interest, and in very preterm and/or VLBW children executive dysfunction has been reported, suggested to arise from disruptions of cortical and subcortical circuits connecting frontal, striatal, and thalamic regions.[6]

The primary aim of this study was to meta-analytically chart the outcome of very preterm and/or VLBW children in terms academic achievement, behavioral functioning and EF. The second aim was to examine the relationship between age at assessment, birthweight and gestational age on the one hand, and effect sizes for the indices of academic achievement, behavioral functioning and EF on the other hand.

METHODS

Inclusion Criteria

The guidelines for reporting meta-analyses of observational studies published by Stroup et al (2000)[15] were taken into account in the design, performance and report of this meta-analysis. We searched original articles employing the search terms child*, low birth weight, prematur*, preterm, outcome, math*, arithmetic, reading, spelling, school, academic, behav*, neurocogn*, and executive function*. The studies were located in the computerized databases PubMed, Psycinfo, and Web-of-Science. The reference lists of published articles were used to identify other relevant articles on these topics.

The literature was reviewed to include studies that met the following inclusion criteria: (1) the study was published between 1998 and 2008, thereby demarcating the period of emerging research into EF, (2) the study concerned both children born very preterm (gestational age ≤ 33 weeks) and/or with VLBW (birthweight ≤ 1500 grams) to estimate the maximal impact of prematurity and VLBW, (3) a case-control design was employed, (4) the mean age at assessment was at least 5 years, since at this age children start to receive formal education which enables academic achievement to be charted, (5) the study reported data on academic achievement, and/or behavioral problems, and/or EF collected with standardized tests, (6) there is a range of different tests and questionnaires available to measure academic achievement, behavioral functioning and EF and some tests or questionnaires may have been used in only one or two studies. Though meta-analytic procedures may be applied with very few studies, the obtained results might then be very unstable.[16] To control for this problem, a cut-off point was chosen of a minimum of five studies that used a particular test or questionnaire, if the study was to be included in the meta-analysis, (7) results were published in English language peer reviewed journals. Studies were excluded if they did not meet all of these inclusion criteria.

Academic Achievement

Fourteen studies[28-34] met the inclusion criteria. Standardized academic achievement tests that were used in these studies all had identical normative scales with age and grade-based standard scores around a mean score of 100 (SD = 15), and included the Woodcock-Johnson Tests of Achievement[17] which measures reading and mathematics; the Wide Range Achievement Test[18] which measures mathematics, reading and spelling; the Wechsler Individual Achievement Test[19] which measures mathematics, reading and spelling, and the Woodcock Reading Mastery Test-Revised[20] which measures reading. Details on the studies included are provided in TABLE 1.

TABLE 1 Studies Reporting on Academic Achievement in Very Preterm and/or VLBW Children

						Academic Achievement Test Scores		
Studies	Participants	GA M (SD)	BW M (SD)	Age M (SD)	Type of Test	Mathematics M (SD)	Reading M (SD)	Spelling M (SD)
Chaudhari et al (2004)[21]	78 VLBW	NA	NA	12.0	WRAT	VLBW=80.4 (15.1)	NA	NA
	90 NC					NC=87.8 (15.8)[a]		
Anderson & Doyle (2003)[22]	250 ELBW	26.7 (1.9)	884.0 (162.0)	8.7 (.3)	WRAT	ELBW=89.2 (14.3)	ELBW=96.6 (16.0)	ELBW=94.4 (12.6)
	217 NC	39.3 (1.4)	3407.0 (443.0)	8.9 (.4)		NC=98.0 (13.4)	NC=103.3 (14.7)	NC=100.0 (13.3)
Grunau et al (2002)[23]	74 Very Preterm	26.0	718.8	9.0 (8.4-12.5)	WRAT	VPT=90.3 (11.0)	VPT=94.5 (16.5)	NA
	30 NC	40.0	3540.0	9.3 (9.0-10.0)		NC=99.9 (10.5)	NC=107.0 (14.1)	
Grunau et al (2004)[24]	53 ELBW	25.8	719.0	17.3 (16.3-19.7)	WRAT	ELBW=91.4 (13.6)[a]	ELBW=103.9 (10.2)[a]	ELBW=100.2 (13.5)[a]
	31 NC	40.0	3506.0	17.8 (16.5–19.0)		NC =106.3 (14.5)[a]	NC=110.6 (10.2)[a]	NC=105.33 (12.2)[a]
Hack et al (2002)[25]	242 VLBW	29.7 (.2)	1179.0 (219.0)	20.0	WJ-TOA	VLBW=89.0 (13.2)[a]	VLBW=95.8 (19.5)[a]	NA
	233 NC	NA	3279.0 (584.0)			NC=95.18 (14.4)[a]	NC=102.7 (21.0)[a]	
Litt et al (2005)[26]	31 <750g	27.7 (2.1)	964.6 (149.6)	11.2 (1.2)	WJ-TOA	VLBW=100.6 (14.4)[a]	VLBW= 101.8 (11.7)[a]	NA
	41 750-1499g	NA	3390.8 (623.6)	11.1 (1.3)	WIAT	NC=105.3 (10.3)[a]	NC=105.3 (12.8)[a]	
	52 NC			11.2 (1.1)				
Kilbride et al (2004)[27]	25 ELBW	26.0 (1.6)	702.0 (76.0)	5.0 (.3)	WRAT	ELBW=74.0 (15.0)	ELBW=81.0 (13.0)	ELBW=69.0 (18.0)
	25 NC	38.8 (1.5)	3215.0 (509.0)			NC= 81.0 (17.0)	NC=87.0 (9.0)	NC=84.0 (18.0)
Rickards et al (2001)[28]	120 VLBW	29.3 (2.0)	1167.0 (215.0)	14.0	WRAT	VLBW=89.0 (13.8)	VLBW=96.8 (14.4)	VLBW=93.7 (16.2)
	41 NC	39.9 (1.0)	3417.0 (432.0)			NC=95.9 (13.6)	NC=100.4 (12.7)	NC=98.6 (13.8)
Saigal et al (2000)[29]	150 Very Preterm	27.0	833.0 (126.0)	14.0 (1.6)	WRAT	VPT=75.0 (18.0)	VPT=85.0 (21.0)	VPT=83.0 (20.0)
	124 NC	NA	3395.0 (483.0)	14.4 (1.3)		NC=92.0 (15.0)	NC=101.0 (15.0)	NC=101.0 (15.0)
Short et al (2003)[30]	75 VLBW	30.0 (2.0)	1256.0 (176.0)	8.0	WJ-TOA	VLBW=98.9 (17.5)[b]	VLBW=100.3 (18.0)[b]	NA
	99 NC	40.0 (1.0)	3451.0 (547.0)			NC=109.3 (17.0)[b]	NC=105.1 (18.0)[b]	
Taylor et al (2006)[31]	219 ELBW	26.4 (.2)	810.0 (124.0)	8.7 (.6)	WJ-TOA	ELBW=88.2 (15.6)	ELBW=88.6 (17.7)	ELBW=88.2 (19.1)
	176 NC	NA	3300.0 (513.0)	9.2 (.8)		NC=98.1 (13.6)	NC=95.7 (13.7)	NC=95.2 (12.7)

TABLE 1 continued

Studies	Participants	GA	BW	Age	Type of	Academic Achievement Test Scores		
						Mathematics	Reading	Spelling
		M (SD)	M (SD)	M (SD)	Test	M (SD)	M (SD)	M (SD)
Taylor et al	65 <750g	25.7 (1.8)	665.6 (68.2)	11.0 (1.1)	WJ-TOA	VLBW=87.6 (24.2)[a]	VLBW=93.9 (18.9)[a]	NA
(2000)[32]	54 750-1499g	29.4 (2.4)	1173.2 (217.1)	11.1 (1.3)		NC=103.2 (12.7)[a]	NC=105.6 (14.8)[a]	
	49 NC	40.0	3360 (660.0)	11.2 (1.2)				
Downie et al	39 Very Preterm	25.8 (1.4)	815.0 (149.0)	11.5 (1.3)	WRMT-R	NA	VPT=94.8 (9.1)	VPT=97.7 (11.4)
(2005)[33]	11 NC	40.6 (1.4)	3842.0 (697.0)	12.1 (1.1)			NC=102.5 (8.4)	NC=107.6 (7.4)
Gross et al	118 Very Preterm	28.3	1164.6	10.1	WIAT	VPT=94.8 (9.0)		
(2001)[34]	119 NC	NA	NA	10.1		NC=96.2 (9.9)		

[a] Means and SDs are weighted

[b] Mean subtest scores are averaged

BW = Birthweight; ELBW = Extremely Low Birthweight; GA = Gestational Age; NA = Not Available; NC = Normal Control; VLBW = Very Low Birthweight; VPT = Very Preterm; WJ-TOA = Woodcock-Johnson Tests Of Achievement; WRAT = Wide Range Achievement Test; WIAT = Wechsler Individual Achievement Test; WRMT-R = Woodcock Reading Mastery Test–Revised

Behavioral Problems

Nine studies[5,24,28,32,36-40] met the inclusion criteria. Standardized questionnaires that were used in these studies included Achenbach's Child Behavior Checklist and Teachers Report Form[35]. For the purposes of the meta-analysis we clustered participants' behavioral problems following the taxonomy developed by Achenbach and colleagues[35] which distinguishes the broad-band scales internalizing behavioral problems (e.g. anxiety or depression) and externalizing behavioral problems (e.g. oppositional behavior). In addition we examined the narrow-band scale attention problems, since very preterm and/or VLBW children have been reported to show these symptoms in particular.[3] In case of missing data, authors were contacted.[5,28,32,36-38] Some authors were not able to provide missing data[5,28] or could not be reached.[39] These studies were therefore not included in the meta-analysis. Details on the nine studies included are provided in TABLE 2.

Executive Function

Twelve publications[28,49-50,53-60] met the inclusion criteria. EF tests that were used in these studies included the Controlled Word Association Test,[41,42] Animal Naming Test,[43] Digit Span,[44,45] and the Trail-Making Test.[46] The Controlled Word Association Test and Animal Naming Test measure letter and semantic fluency, respectively, which are both components of verbal fluency. Verbal fluency is the ability to quickly generate as many different solutions for a particular (verbal) problem as possible,[42] and also involves heavy linguistic requirements. Both tests were used in each of the studies on verbal fluency and are identical in test administration, response mode, and scoring,[42] and for the purposes of this meta-analysis, a mean verbal fluency score was calculated for each study. Digit Span is a test of working memory, in which series of digits are read aloud to the child.[47] Digits Forward requires repetition of series of digits in the same order, whereas Digits Backward requires repetition of series of digits in reverse order.[47] The total number of correctly repeated series on Digits Forward and Backward served as an index for working memory. Trail-Making Test is a test that measures cognitive flexibility[48] and involves switching between mental sets.[42] In part A of this test, the child needs to draw lines to connect consecutively numbered circles. In Part B of this test, the child has to connect consecutively numbered circles and lettered circles while alternating between the two sequences.[42] The score on the Trail-Making test part B served as an index for cognitive flexibility.

If data of two measurements pertaining to a partially overlapping sample had been reported,[49] results of the first measurement were included in our meta-analysis in order to avoid retest effects that would confound our results. Studies were excluded if they did not report scores for either the Controlled Word Association Test and/or the Animal Naming Test, separately.[50,51] Details on the studies included are provided in TABLE 3.

TABLE 2 Studies Reporting on Behavioral Problems in Very Preterm and/or VLBW Children

Studies	Participants	GA M (SD)	BW M (SD)	Age M (SD)	Questionnaire	Externalizing Problems	Internalizing Problems	Attention Problems
Greenley et al	48 <750g	25.8 (1.8)	660.3 (72.8)	11.2 (1.5)	CBCL	VLBW=47.9 (9.7)	VLBW=49.9 (10.1)	NA
(2007)[40]	46 750-1499g	29.4 (2.4)	1169.0 (215.1)	11.1 (1.3)		NC=48.1 (11.5)	NC=49.6 (11.6)	
	51 NC			11.2 (1.3)	TRF	VLBW=51.2 (8.8)	VLBW=52.3 (8.6)	
						NC=50.4 (8.0)	NC=51.2 (8.7)	
Farooqi et al	83 EPT	24.6 (0.7)	765.0 (111.0)	10.9 (.8)	CBCL	ELBW=50.9 (12.8)	ELBW=57.5 (16.8)	ELBW=61.7 (16.8)
(2007)[36]	86 NC	39.2 (2.7)	3520.0 (601.0)	11.6 (.8)		NC=49.2 (13.0)	NC=48.8 (8.8)	NC=51.5 (13.9)
					TRF	ELBW=52.5 (12.7)	ELBW=55.4 (10.4)	ELBW=56.8 (11.6)
						NC=50.0 (9.9)	NC=50.0(9,9)	NC=50.0 (9.9)
Grunau et al	53 ELBW	25.8	719.0	17.3 (16.3-19.7)	CBCL	ELBW=50.1 (11.2)	ELBW=53.7 (11.3)	ELBW=57.8 (8.2)
(2004)[24]	31 NC	40.0	3506.0	17.8 (16.5–19.0)		NC=44.0 (8.9)	NC=46.9 (14.5)	NC=51.6 (3.1)
Weindrich et al	29 VLBW	30.7 (2.0)	1212.0 (185.0)	10.9 (.1)	CBCL	VLBW=51.6 (8.2)	VLBW=53.5 (11.6)	VLBW=58.1 (9,8)
(2003)[38]	112 NC	39.9 (1.1)	3344.0 (382.0)	10.9 (.2)		NC=51.3 (10.4)	NC=52.6 (8.8)	NC=54.6 (6.7)
						VLBW=49.7 (8.1)	VLBW=54.9 (11.7)	VLBW=54.7 (5.6)
						NC=51.1 (9.7)	NC=51.1 (9.5)	NC=53.4 (5.4)
Saigal et al	141 ELBW	27.0 (2.4)	838.0 (123.0)	14.1 (1.5)	CBCL	NA	NA	NA
(2003)[5]	122 NC	NA	3391.0 (48.0)	14.4 (1.2)				
Rickards et al	120 VLBW	29.3 (2.0)	1167.0 (215.0)	14.0	CBCL	NA	NA	NA
(2001)[28]	41 NC	39.9 (1.0)	3417.0 (432.0)	14.0				
Nadeau et al	61 EPT	27.4 (1.1)	1024.3 (204.2)	7.0	CBCL	EPT=50.9 (8.8)	EPT=52.4 (10.0)	EPT=57.7 (8.7)
(2001)[37]	44 NC	39.8 (1.6)	3453.4 (497.8)		TRF	NC=53.3 (9.7)	NC=53.3 (10.6)	NC=56.1 (8.3)
						EPT=50.5 (8.4)	EPT=54.4 (9.2)	EPT=55.3 (7.4)
						NC=50.9 (9.7)	NC=53.3 (10.3)	NC=53.1 (5.1)

TABLE 2 continued

						Behavioral Problems		
Taylor et al	60 <750g	25.7 (1.8)	665.6 (68.2)	11.0 (1.1)	CBCL	VLBW=48.4 (9.8)	VLBW=49.6 (9.9)	VLBW=56.9 (8.4)
(2000)[32]	55 750-1499g	29.4 (2.4)	1173.2 (217.1)	11.0 (1.3)	TRF	NC=46.6 (11.1)	NC=48.0 (11.4)	NC=52.4 (5.1)
	49 NC	40.0	3360 (660.0)	11.0 (1.2)		VLBW=51.5 (8.9)	VLBW=52.7 (8.6)	VLBW=56.0 (7.2)
						NC=50.2 (8.0)	NC=51.0 (8.0)	NC=53.7 (5.3)
Stjernqvist &	61 EPT	27.1 (1.1)	1042 (252.0)	10.5 (.6)	CBCL	NA	NA	NA
Svenningsen	61 NC	40.1 (1.4)	3648 (533.0)	10.6 (.6)				
(1999)[39]								

BW = Birthweight; ELBW = Extremely Low Birthweight; EPT = Extremely Preterm; GA = Gestational Age; gr = grams; NA = Not Available; NC = Normal Controls; VLBW = Very Low Birthweight

TABLE 3 Studies Reporting on Executive Function in Very Preterm and/or VLBW Children

Studies	Participants	GA M (SD)	BW M (SD)	Age M (SD)	Type of Test	Executive Function Domain	Test Scores M (SD)
Narberhaus et al (2008)[53]	52 Very Preterm	29.7 (2.0)	1273.0 (337.7)	14.2 (1.7)	COWAT	Phonetic Fluency	28.0 (7.9)
	50 NC	39.6 (1.5)	3421.0 (428.0)	14.3 (2.2)			33.2 (10.4)
Narberhaus et al (2008)[53]	52 Very Preterm	29.7 (2.0)	1273.0 (337.7)	14.2 (1.7)	TMT Trails B	Cognitive Flexibility	54.4 (26.7)
	50 NC	39.6 (1.5)	3421.0 (428.0)	14.3 (2.2)			41.2 (21.3)
Narberhaus et al (2008)[53]	52 Very Preterm	29.7 (2.0)	1273.0 (337.7)	14.2 (1.7)	Digit Span	Working Memory	9.5 (3.4)
	50 NC	39.6 (1.5)	3421.0 (428.0)	14.3 (2.2)			11.2 (2.6)
Narberhaus et al (2008)[53]	52 Very Preterm	29.7 (2.0)	1273.0 (337.7)	14.2 (1.7)	ANT	Category Fluency	19.0 (5.1)
	50 NC	39.6 (1.5)	3421.0 (428.0)	14.3 (2.2)			21.5 (4.2)
Nosarti et al (2007)[54]	61 Very Preterm	29.5 (1.8)	1296.0 (295.8)	22.3 (1.1)	COWAT	Phonetic Fluency	39.3 (13.0)
	64 NC	NA	NA	23.2 (1.5)			50.8 (13.5)
Nosarti et al (2007)[54]	61 Very Preterm	29.5 (1.8)	1296.0 (295.8)	22.3 (1.1)	ANT	Category Fluency	43.7 (13.2)
	64 NC	NA	NA	23.2 (1.5)			50.5 (12.6)
Nosarti et al (2007)[54]	61 Very Preterm	29.5 (1.8)	1296.0 (295.8)	22.3 (1.1)	TMT Trails B	Cognitive Flexibility	66.4 (24.5)
	64 NC	NA	NA	23.2 (1.5)			56.6 (19.0)
Allin et al (2007)[49]	94 Very Preterm	NA	NA	15.5 (.7)	ANT	Category Fluency	19.9 (5.3)
	44 NC			15.0 (.7)			19.3 (4.6)
Allin et al (2007)[49]	94 Very Preterm	NA	NA	15.5 (.7)	COWAT	Phonetic Fluency	28.7 (9.0)
	44 NC			15.0 (.7)			32.9 (8.9)
Shum et al (2008)[52]	45 Very Preterm	26.4 (1.9)	838.2 (151.7)	8.3 (.9)	TMT Trails B	Cognitive Flexibility	84.7 (43.7)
	49 NC	39.9 (1.5)	3577.8 (516.5)	8.2 (.9)			63.3 (42.1)
Caldu et al (2006)[55]	25 Very Preterm	29.5 (2.5)	NA	13.4 (1.9)	COWAT	Phonetic Fluency	27.1 (8.4)
	25 NC	39.9 (1.4)		13.9 (2.5)			32.1 (11.8)
Caldu et al (2006)[55]	25 Very Preterm	29.5 (2.5)	NA	13.4 (1.9)	ANT	Category Fluency	16.4 (4.1)
	25 NC	39.9 (1.4)		13.9 (2.5)			21.3 (4.1)

TABLE 3 continued

Studies	Participants	GA M (SD)	BW M (SD)	Age M (SD)	Type of Test	Executive Function Domain	Test Scores M (SD)
Gimenez et al (2006)[56]	30 Very Preterm	29.1 (2.0)	1107.8 (240.3)	14.3 (2.0)	COWAT	Phonetic Fluency	28.0 (8.5)
	30 NC	NA	NA	14.1 (2.0)			32.6 (8.8)
Gimenez et al (2006)[56]	30 Very Preterm	29.1 (2.0)	1107.8 (240.3)	14.3 (2.0)	ANT	Category Fluency	16.7 (3.6)
	30 NC	NA	NA	14.1 (2.0)			21.2 (4.7)
Kulseng et al (2006)[57]	54 VLBW	28.9 (2.7)	1178.0 (234.0)	14.1 (.3)	TMT Trails B	Cognitive Flexibility	46.7 (22.0)
	83 NC	39.6 (1.2)	3690.0 (458.0)	14.2 (.3)			31.9 (18.6)
Anderson & Doyle (2004)[58]	298 ELBW/Very Preterm	26.7 (1.9)	884.0 (162.0)	8.7 (.3)	Digit Span	Working Memory	8.5 (2.8)
	223 NC	39.3 (1.4)	3407.0 (443.0)	8.9 (.4)			9.5 (2.9)
Foulder-Hughes & Cooke (2003)[59]	280 Very Preterm	29.8 (23.0-32.0)	1467.0 (424.0)	7.5	Digit Span	Working Memory	8.6 (2.7)
	210 NC	-	-	7.5			10.0 (3.0)
Rushe et al (2001)[50]	75 Very Preterm	29.6 (1.8)	1299.0 (284.0)	14.9 (.4)	TMT Trails B	Cognitive Flexibility	75.0 (24.5)
	53 NC	NA	NA	14.9 (.6)			69.2 (25.2)
Rickards et al (2001)[28]	120 VLBW	29.3 (2.0)	1167.0 (215.0)	14.0	Digit Span	Working Memory	9.9 (3.6)
	41 NC	39.9 (1.0)	3417.0 (432.0)				9.8 (3.6)
Rushe et al (2001)[50]	75 Very Preterm	29.6 (1.8)	1299.0 (284.0)	14.9 (.4)	Digit Span	Working Memory	13.6 (2.9)
	53 NC	NA	NA	14.9 (.6)			14.2 (4.1)
Olsen et al (1998)[60]	42 Very Preterm	31.0	1410.0	8.0	Digit Span	Working Memory	9.3 (2.1)
	42 NC	39.0	3323.0				9.9 (2.6)

ANT = Animal Naming Test; COWAT = Controlled Word Association Test; NA = Not Available; NC = Normal Control; TMT = Trail Making Test part B

Statistical Analyses

Meta-analysis was conducted using the computer program Comprehensive Meta-Analysis.[61] For studies that reported results for subgroups of very preterm and/or VLBW children or controls, we calculated a weighted group mean and weighted SD by multiplying each subgroup mean and SD, respectively, by its sample size, adding the subtotals, and dividing the obtained sum by the total sample size.[24,25,32-34,51] Most dependent measures were not standardized. Hence, the variability metric for the dependent measures differed both between studies as well as between groups within studies (very preterm and/or VLBW children and controls). We therefore calculated effect sizes and 95% confidence intervals in terms of Cohen's *d* for each study separately. Cohen's *d* is defined by the difference between two means divided by the pooled SD for those means.[62] Combined effect sizes for each of the dependent variables of the three outcome domains were computed by weighting the domain-specific effect sizes by the studies' sample sizes. Cohen's guidelines were followed to indicate the strength of the combined effect sizes, with 0.20, 0.50, and 0.80 referring to small, medium, and large effect sizes, respectively.[62]

Q-test statistics[63] were performed to test homogeneity among the studies' effect sizes (i.e. whether findings are consistent among studies), and among combined effect sizes for the various indices of academic achievement, behavioral problems and EF.

Pearson's correlation coefficients (*r*) were calculated to test the impact of mean birthweight, mean gestational age, as well as mean age at assessment, on the strength of the studies' effect sizes for all indices of academic achievement, behavioral problems and EF. Cohen's guidelines were followed to indicate the strength of the correlation coefficients, with 0.10, 0.30, and 0.50 referring to small, medium, and large coefficients, respectively.[66]

A major concern in conducting meta-analyses is the existence of publication bias. Publication bias is that studies reporting non-significant results failed to be published and therefore are not included in a meta-analysis. If these studies had been included, they would nullify observed effects.[16] We examined the potential for publication bias using two methods. First, we computed Rosenthal's fail-safe N[16] (i.e. the number of studies that would be required to nullify the observed effect) for each combined effect size, separately. A fail-safe N is often considered robust if it is greater than 5k+ 10 (k = number of studies in the meta-analysis).[16] Second, we correlated sample sizes to the effect sizes. A negative correlation between sample sizes and effect sizes indicates that small studies with significant results may be published more often than small studies with non-significant results, which has recently been shown to exist in 80% of the meta-analyses.[67]

RESULTS

TABLE 4 depicts the sample sizes, number of studies, combined effect sizes in terms of Cohen's d, 95% confidence intervals, Q-test statistics, fail-safe Ns, and correlations with sample sizes, for effect sizes pertaining to academic achievement, behavioral problems and EF.

Academic Achievement

Mathematics, reading and spelling were significantly poorer in very preterm and/or VLBW children. Combined effect sizes were -0.48 for reading, -0.60 for mathematics, and -0.76 for spelling. The combined effect sizes for mathematics and spelling were medium to close to large and did not differ significantly (Q(1) = 2.41, $p = 0.12$). The combined effect size for reading, however, was significantly lower than the combined effect sizes for mathematics (Q(1) = 5.73, $p = 0.02$), and spelling (Q(1) = 12.47, $p < 0.001$). Within each of the indices for academic achievement, strength of the studies' effect sizes varied significantly between studies ($p_s < 0.01$). Fail-safe Ns ranged from 355 to 705, and small to medium, albeit non-significant correlation coefficients were observed between sample sizes and indices for academic achievement (all *p*s > 0.32), indicating that there was no evidence for publication bias.

Behavioral Problems

Parents and teachers did not differ significantly in their ratings of internalizing behavioral problems (Q(1) = 0.02, $p = 0.88$), externalizing behavioral problems (Q(1) = 0.007, $p = 0.93$), and attention problems (Q(1) = 1.95, $p = 0.16$).

Significant (*p*s < 0.001) and close to medium combined effect sizes were found for parent and teacher ratings of attention problems: -0.59 and -0.43, respectively. Small combined effect sizes were found for parent and teacher ratings of internalizing behavioral which were -.20 ($p < 0.01$), and -.28 ($p = 0.16$), respectively, and for externalizing behavioral problems, which were -0.08, and -0.09 and not significant (*p*s > 0.22). Parent and teacher ratings for attention problems were significantly larger than parent and teacher ratings of externalizing and internalizing behavioral problems (Q(1) > 12.09, $p < 0.001$). Within parent and teacher ratings, combined effect sizes for attention problems, internalizing behavioral and externalizing behavioral problems did not differ significantly (Q(1) < 3.03, *p*s > 0.08). Except for parent ratings of internalizing behavioral problems, findings were consistent across studies.

Fail-safe Ns for parent and teacher ratings of internalizing behavioral problems were 18 and 10, respectively; for parent and teacher ratings of externalizing behavioral problems

TABLE 4 Sample Sizes, Number of Studies, Combined Effect Sizes in Terms of Cohen's *d*, 95% Confidence Intervals, Heterogeneity Statistics, Correlations with Sample Sizes, and Fail-safe *N*s for Outcome Measures

	Sample Sizes	Number of Studies	*d*	*95%* CI	P	Q	P	Fs N	r
Academic Achievement									
Mathematics	2753	13	-.60	-.74, -.46	< .001	34.59	< .001	705	.03
Reading	2639	13	-.48	-.60, -.34	< .001	26.21	.01	417	.31
Spelling	1251	8	-.76	-1.13, -.40	< .001	80.76	< .001	355	.22
Behavioral Problems									
CBCL Internalizing	930	6	-.20	-.48, .08	.16	17.63	< .001	18	-.16
TRF Internalizing	920	5	-.28	-.45, -.12	< .01	4.32	.37	10	-.54
CBCL Externalizing	930	6	-.09	.05, .22	.22	8.64	.13	3	.26
TRF Externalizing	920	5	-.08	-.24, .07	.30	2.46	.65	0	-.87
CBCL Attention	930	5	-.59	-.74, -.44	< .001	6.95	.14	67	-.13
TRF Attention	920	4	-.43	-.61, -.25	< .001	2.76	.43	17	-.74
Executive Function									
Verbal Fluency	475	5	-.57	-.82, -.32	< .001	6.70	.15	41	.81
Working Memory	1580	7	-.36	-.47, -.20	< .001	9.09	.17	56	.33
Cognitive Flexibility	586	5	-.49	-.66, -.33	< .001	4.03	.41	39	-.06

Note. Negative effect sizes indicate underperformance on academic achievement and EF tests, and higher ratings of behavioral problems for very preterm and/or VLBW children in comparison to controls.

CBCL = Child Behaviour Checklist; CI = confidence interval; Fs *N* = fail-safe *N*; TRF = Teachers Report Form

3 and 0, respectively; and for parent and teacher ratings of attention problems 67 and 17, respectively. Non-significant, small correlations were observed between sample sizes and parent ratings of internalizing, and externalizing behavior problems, and attention problems (all *p*s > 0.61). Non-significant, albeit large and negative correlations were observed between sample sizes and teacher ratings of internalizing and externalizing behavior problems, and attention problems (all *p*s > 0.08). The results point to possible publication bias in studies on teacher ratings of problem behavior.

Executive Function

Verbal fluency (Controlled Word Association Test and Animal Naming Test), working memory (Digit Span), and cognitive flexibility (Trail-Making Test part B), were significantly poorer in children born very preterm and/or with VLBW than in controls. The combined effect sizes were small to medium and were -0.36 for working memory, -0.49 for cognitive flexibility, and -0.57 for verbal fluency (all *p*s < 0.001). Differences between the combined effect sizes for these indices of EF were not significant (Q(2) = 6.33, p = 0.10). Within these indices of EF, effect sizes did not vary significantly between studies (all *p*s > 0.15). Fail-safe Ns ranged from 39 to 56. Correlations observed between sample sizes and effect sizes for EF ranged from small (r = -0.06) to large (r = 0.81), however were not significant (all *p*s > 0.10). There was no clear evidence for publication bias.

Age at Assessment

TABLE 5 displays Pearson's correlation coefficients for the relationship between mean age at assessment and the studies' effect sizes for academic achievement, behavioral problems and EF. All correlation coefficients for the relationship between effect sizes for academic achievement and mean age at assessment (5.0-20.0 years), and EF and mean age at assessment (7.5-22.3 years), were small and not significant (all *r*s < -0.19, all *p*s > 0.55). After exclusion of one extreme effect size[45] which would confound the results, correlations between parent and teacher ratings of internalizing, externalizing and attention problems, and mean age at assessment (5.9-17.3 years) ranged from small to large, though were not significant (all *r*s < -0.56, all *p*s > 0.33).

Birthweight and Gestational Age

TABLE 5 displays Pearson's correlation coefficients for the relationship between mean birthweight and mean gestational age, and studies' effect sizes for academic achievement, behavioral problems and EF. Mean birthweight (702-1265 g) and mean gestational age (25.8-30.0 weeks) were strongly and positively correlated with studies' effect sizes for mathematics and reading (all *r*s > 0.51, all *p*s < 0.05). After exclusion of one extreme effect size,[34] correlations between mean birthweight (702.0-1176.0 g), mean

TABLE 5 Pearson's Correlation Coefficients Between Outcome Measures and Age at Assessment, Birthweight, and Gestational Age

		N	Age		BW[a]		GA[a]	
			r	*P*	*r*	*P*	*r*	*P*
Academic Achievement								
Mathematics		11	-.19	.55	.60	.02	.51	.05
Reading		13	.09	.77	.70	.01	.65	.01
Spelling		8	-.16	.72	.43[b]	.17[b]	.42[b]	.18[b]
Behavioral Problems								
CBCL	Internalizing	6	-.56[b]	.33[b]	.71	.06	.82	.03
TRF	Internalizing	5	-.54	.35	.18	.39	.25	.34
CBCL	Externalizing	6	-.37[b]	.54[b]	.56	.13	.47	.18
TRF	Externalizing	5	-.06	.93	.98	.002	.93	.01
CBCL	Attention	5	-.47[b]	.53[b]	.71	.09	.45	.23
TRF	Attention	4	-.31	.70	.91	.05	.94	.03
Executive Function								
Verbal Fluency		5	-.04	.95	NA[c]	NA[c]	NA[c]	NA[c]
Working Memory		7	.33	.47	.43[b]	.24[b]	.03	.48
Cognitive Flexibility		5	.17	.79	.24	.35	.19	.38

Note. Significant and trend correlations are shown in bold type.

BW = Birthweight; CBCL = Child Behavior Checklist; GA = Gestational Age; *N* = number of studies; NA = Not Available; TRF = Teachers Report Form

[a]Given the hypothesis that a decrease in birthweight and gestational age is associated with higher combined effect sizes, and the fact that the small number of studies included for some indices might reduce statistical power, one-tailed tests of significance were conducted.

[b]Results after omission of one extreme effect size.

[c]Correlation coefficients for verbal fluency were not calculated as the values for gestational age for the pertinent studies ranged from 29.0 to 30.0 weeks, and the values for birthweight ranged from 1107.0 to 1296.0 grams; findings might therefore be unreliable due to restriction of range.

gestational age (25.8-29.3 weeks) and spelling were small and not significant (*r*s < 0.43, *p*s > 0.17).

Mean gestational age (24.6-30.7 weeks) was strongly and positively correlated with parent ratings of internalizing behavior problems, and teacher ratings of externalizing behavioral problems and attention problems (all *r*s > 0.82, all *p*s < 0.03). Mean birthweight (765.0-1212.0 g) was strongly and positively correlated with teacher ratings of externalizing behavioral problems and attention problems (*r*s > 0.91, *p*s < 0.05). There was a trend towards a significant association between mean birthweight (719.0-1212.0 g) and parent ratings of internalizing behavioral problems (*r*s = .71, *p*s > .06), and attention problems (*r*s = 0.71, *p*s > 0.09). Mean birthweight (719.0-1212.0 g) was not correlated with effect sizes for teacher ratings of internalizing problems, and parent ratings of externalizing problems, and mean gestational age (24.6-30.7 weeks) was not correlated with effect sizes for teacher ratings of internalizing behavioral problems, and parent ratings of externalizing behavioral and attention problems (all *r*s < 0.56, all *p*s > 0.13).

Correlation coefficients for verbal fluency were not calculated, as the obtained results might be unreliable due to restriction of range for birthweight and gestational age. After exclusion of one extreme effect size[28] which would confound the results, mean birthweight (838.3-1467.0 g) and mean gestational age (26.4-31.0 weeks) were not significantly correlated with effect sizes for working memory (*r*s < 0.43, *p*s > 0.24). Mean birthweight (838.3-1299.0 g) and mean gestational age (26.4-29.7 weeks) were not correlated with effect sizes for cognitive flexibility (all *r*s < 0.24, all *p*s > 0.35).

DISCUSSION

This meta-analysis provides sound evidence for the presence of major difficulties in academic achievement, symptoms of inattention, internalizing behavioral problems and poor EF, in very preterm and/or VLBW children in comparison to controls. The results show that very preterm and/or VLBW children were 0.48 SD to 0.76 SD behind their term born peers in reading, mathematics and spelling which translates into a 7.2 to 11.4-point decrement for these key academic achievement areas. Spelling was found to be just as compromised as mathematics; differences between both combined effect sizes were not significant. Previous research has suggested that mathematics was the most pronounced academic achievement deficit,[2,29] thereby overlooking the major spelling difficulties of very preterm and/or VLBW children.

Attention problems were most pronounced in very preterm and/or VLBW children with teacher and parent ratings being 0.43 SD to 0.59 SD, respectively, higher than for controls. Teachers also reported significantly more internalizing behavior problems for these children than for peers. It should be noted, however, that the results for teacher reported problem behavior should be interpreted cautiously as there was some evidence for publication bias. Parents and teachers did not differ significantly in their ratings of behavioral problems for very preterm and/or VLBW children. This does, however, not imply a high level of agreement at the individual level between informants. Our results indicate that internalizing problems (i.e. withdrawn behavior and symptoms of depression) do occur in these children, but that these symptoms are not as prominent as symptoms of inattention. This meta-analysis did not find significantly increased parent and teacher ratings of externalizing problems (i.e. delinquent and risk-taking behaviors) in very preterm and/or VLBW children in comparison to their term born peers, though in a previously conducted meta-analysis by Bhutta et al[3] it was found that 69% of the studies included reported a high prevalence of externalizing behavioral problems. Unclear is, however, whether Bhutta et al[3] have subsumed attention problems under externalizing behavioral problems. In addition, Bhutta et al[3] conducted a narrative review on behavior and did not take a quantitative meta-analytic approach which precludes comparison of their results with our findings.

This meta-analytic study was the first to aggregate studies on the neurocognitive domain EF. Although EF covers a variety of capabilities, the majority of studies into very preterm and/or VLBW children have focused on verbal fluency, working memory, and cognitive flexibility, thereby allowing meta-analytic aggregation of findings. Our results show that very preterm and/or VLBW children score 0.36 SD to 0.57 SD lower than their term born peers on these measures, differences that translate into a small to medium effect sizes. These findings indicate that very preterm and/or VLBW children display difficulties in holding information in mind, switching between mental sets, and generating as many different solutions for a particular problem as possible. These EFs have been strongly related to academic achievement and/or behavioral functioning[10-12,69] and might form an explanation of the problems that very preterm and/or VLBW children face in these domains of functioning. However, other well-established EFs of importance for academic and behavioral functioning, such as inhibitory control, which has been considered as the underlying symptoms of inattention,[11] have only scarcely been assessed in these children. Therefore, in the search towards the understanding of academic underachievement and behavioral problems in very preterm and/or VLBW children, insight into other EF domains may be of great merit.

Smaller and more premature infants were found to be more prone to poor academic achievement, as well as internalizing and externalizing behavior problems than more mature and heavier peers. Despite the small number of studies included in the correlational analyses, significant results were obtained. This bolsters our findings and underlines the importance of birthweight and gestational age as a predictor for later development. Such an inverse relationship has previously been demonstrated for the incidence of major disabilities in very preterm and/or VLBW children,[73] and is related to the risk for disruption in cortical development (corticogenesis) and brain connectivity, which increases when birthweight and gestational age decrease.[74] For the extreme preterm or extreme low birthweight (ELBW) infants, adverse concomitant sequelae (such as abnormal cerebral ultrasound findings, chronic lung disease, and postnatal steroid administration), may explain abnormal neurodevelopmental outcomes in addition to birthweight and gestational age.[75,76]

It has been questioned whether academic underachievement, behavioral problems and neurocognitive dysfunction in very preterm and/or VLBW children improve or worsen over time.[6] Some studies have found evidence in support for the idea that the gap between very preterm and/or VLBW children and term born peers becomes smaller with increasing age.[50,77] Others have compared outcomes at school age and in young adulthood and have suggested that very preterm and/or VLBW teens and young adults continue to lag behind term born peers in terms of cognitive and academic achievement.[25,29] Our results showed that the strength of the studies' effect sizes was not significantly related to age at assessment, which suggests that the disadvantage in academic achievement, behavioral sequelae, and neurocognitive function, at least for the age range studied (5.0-22.3 years), remains stable during development, and persists into young adulthood. It should be noted that the number of studies retrieved assessing very preterm and/or VLBW young adults is scarce (n = 4), and studies in this age group are greatly needed. At the same time, it has been found that very preterm young adults are not less satisfied with their lives and do not have lower self-esteem than their peers[4]. Possibly family and environmental factors might alter the subjective experience of the impairments faced by very preterm and/or VLBW young adults.[68]

This meta-analysis has some limitations which need to be considered. It should be noted that some of the correlational analyses were conducted on a small of number of studies and therefore have limited power; results may change if more studies would have been included. For the purpose of this meta-analytic study, we assumed that academic achievement test scores derived from different measures of academic achievement were comparable because of identical normative scales (M = 100, SD = 15). This assumption, however, overlooks the possible differences between tests in terms of content, and may possibly explain part of the heterogeneity among the effect sizes obtained. In addition, our exclusive focus on internalizing and externalizing problems, as well as attention problems, might have disregarded other types of behavioral problems. Our inclusion criteria did not take the attrition rates of studies into account, however correlational analyses showed that there was no significant relationship between studies' effect sizes and attrition rates (not reported; details available from the first author). Finally, we included children on the basis of birthweight and gestational age which may have caused heterogeneity between studies. However inclusion of studies on the basis of birthweight or gestational age exclusively would have resulted in a limitation of the number of studies available for this meta-analysis.

In conclusion, this meta-analysis quantitatively aggregated studies into the outcomes of very preterm and/or VLBW children in terms of multiple indices of academic achievement, behavioral functioning and EF. It combines results from different countries.

Despite the cross-cultural differences existing in such a comparison, it provides evidence from a large number of participants that very preterm and/or VLBW children show severe deficits in mathematics, reading and spelling and poor EF, and face behavioral sequelae in terms of symptoms of inattention and internalizing behavioral problems. These adverse outcomes were demonstrated to persist into young adulthood and were inversely related to birthweight and gestational age. Our findings highlight the need for long-term follow-up for prematurity and VLBW survivors. In addition, having clearly established these childrens' areas of weakness, research needs to move on to study underlying dysfunctions and focus on feasibility and efficacy of intervention strategies to minimize the long-term impact of prematurity and VLBW.

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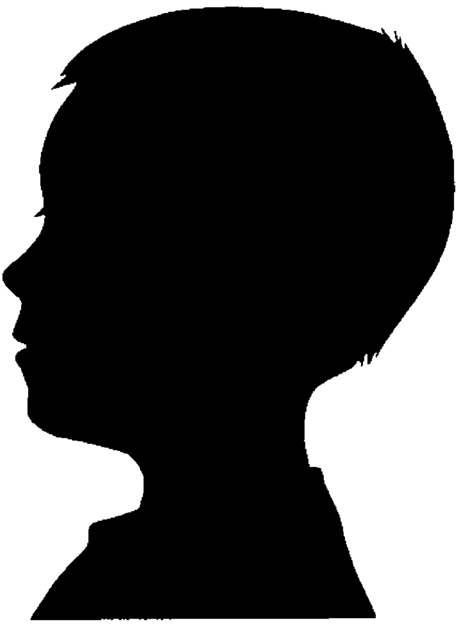
Chapter 3

Development of preschool and academic skills in very preterm children

Journal of Pediatrics 2011; 158: 51-56



ABSTRACT

Objective

To examine performance in preschool and academic skills in very preterm (gestational age ≤ 30 weeks) and term-born comparison children aged 4 to 12 years.

Methods

Two-hundred very preterm children (mean age = 8.2 ± 2.5) born between 1996 and 2004 were compared to 230 term-born children (mean age = 8.3 ± 2.3). The Dutch National Pupil Monitoring System was used to measure preschool numerical reasoning and early linguistics, and primary school simple and complex word reading, reading comprehension, spelling, and mathematics/arithmetic. Univariate analyses of variance assessed the effects of preterm birth on performance across grades and on grade retention.

Results

In preschool, very preterm children performed comparable to term-born children in early linguistics, but perform poorer (0.7 SD) in numerical reasoning skills. In primary school, very preterms scored 0.3 SD lower in complex word reading and 0.6 SD lower in mathematics-arithmetic, but perform comparable to peers in reading comprehension and spelling. They had a higher grade retention rate (25.5%), though grade retention did not improve their academic skills.

Conclusions

Very preterm children do well in early linguistics, reading comprehension, and spelling, but have clinically significant deficits in numerical reasoning skills and mathematics-arithmetic, which persist over time.

INTRODUCTION

Very preterm (gestational age ≤ 30 weeks) children that survive without severe disabilities[1] are risk for poorer academic achievement, [2] showing a higher grade retention rate and need for special education services. In a recently conducted meta-analysis we demonstrated that very preterm children are 0.48 SD to 0.76 SD behind term born peers in reading, mathematics and spelling; deficits that persist into young adulthood.[2] Smaller and more premature infants are more prone to poor academic achievement than their more mature and heavier peers.[2]

The development of academic skills already starts before formal schooling in first grade.[3,4] Studies with healthy term born children have shown that some basic level of pre-academic skills is required for mastering later academic abilities.[4,5] Information on preschool skills in very preterm children affecting later academic achievement is lacking. In addition, few studies[6,7] have assessed academic achievement at an early school age when very preterm children enter primary school. It is not sufficiently known whether poor academic achievement in very preterm children becomes apparent yet in the beginning of primary school or as these children grow older.

The aim of this study was to report the development of preschool and academic skills in a large sample of very preterm children aged 4 to 12 years in comparison to that of a term-born group comparable in age and gender. Preschool and academic achievement was assessed using the Dutch National Pupil Monitoring System that comprises a comprehensive series of tests measuring preschool and academic skills and offers a unique possibility to study these skills in detail. This study compares rates of grade retention as well as levels of academic performance between children born very preterm and full-term aged 4 to 12 years. Performance in pre- and primary school grades and the effect of grade retention on performance was examined.

METHODS

Participants and Selection Procedure

The flow-chart in FIGURE 1 describes the inclusion procedure of very preterm children. The final study sample of 200 very preterm (gestational age ≤ 30 weeks) children was derived from all (n = 706) very preterm surviving singletons admitted between 1996-2004 to the neonatal intensive care unit (NICU) of the Erasmus University Medical Center-Sophia Children's Hospital Rotterdam, The Netherlands. Twins were excluded as inclusion of these children would violate the assumption of independence of data.

Disabilities were classified according to Wood et al.[8] A "severe disability" was defined as one that was likely to put the child in need of physical assistance to perform daily activities. [8] Children with severe disabilities are not able to perform tests as employed in the present study. These children were traced on the basis of their medical records and were not included in the study. For the remaining children, a postcard introducing the study was sent to the parents that could be traced informing them that one of the

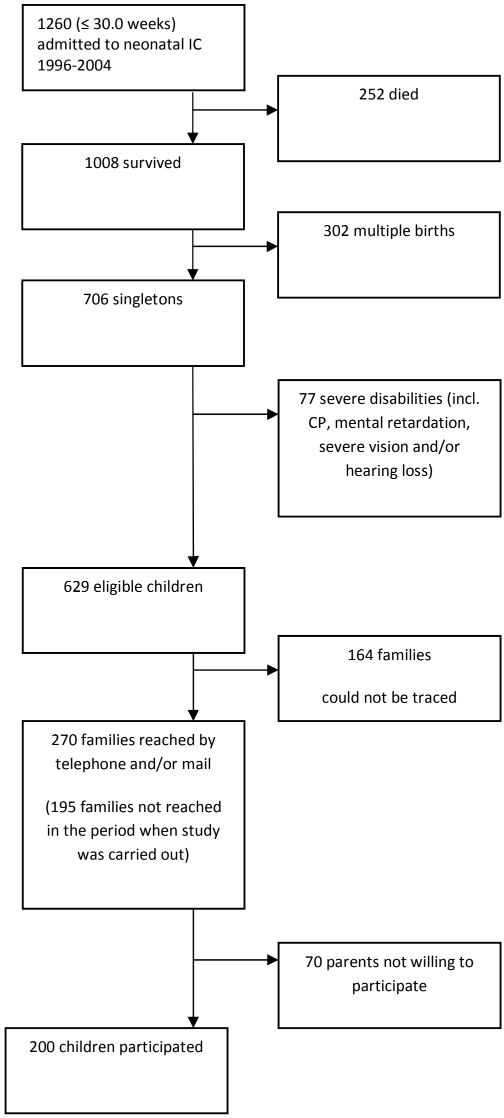


FIGURE 1 Flow-Chart of Inclusion of the Very Preterm Group

investigators would be calling in the next 2 weeks to ask permission for the child's participation. The present study was carried out in 2007 and 2008. In this time period, 270 parents could be reached.

Very preterm children who participated (n = 200) did not differ from children who did not participate (n = 629) with respect to gestational age, birthweight, duration of NICU-stay (all Fs < 1.6, all ps > 0.2), or gender (χ^2 = 2.1; p = 0.2). Very preterm children whose parents were not willing to participate (n=70) did not differ from the final sample of very preterm children (n=200) with respect to gestational age, duration of NICU-stay (Fs < 0.5, ps > 0.5), or gender (χ^2 = 0.3, p = 0.6), although there was a small difference in birthweight (F = 5.1, p = 0.03). There were no differences with respect to these neonatal characteristics between the included year cohorts (each year cohort was compared with all other year cohorts, all Fs < 0.8; all ps > 0.6).

A comparison group was recruited from three regular primary schools located in the same neighborhoods as schools attended by the very preterm children. Parents of all children attending these three schools were invited to participate by a letter. All parents that gave permission for their child to participate signed informed consent, gave information on perinatal characteristics, neurological functioning, and the presence of minor disabilities. In the comparison group, only children without histories of prematurity (gestational age > 37 weeks), perinatal complications, neurological disorders, were included.

Minor disabilities as observed in the participating children are presented in TABLE 1 and included (1) vision corrected to normal with contact lenses, (2) hearing loss corrected to normal with hearing aids, (3) spastic unilateral cerebral palsy (CP), classified according to standards of the Surveillance of Cerebral Palsy in Europe (SCPE, 2000).

Dutch School System

In the Netherlands, preschool starts at the child's fourth birthday and constitutes two years. Primary school starts with grade 1 in August for children who turn 6 years of age between October of the previous year and the following September. Children born in July to September are, usually because of social/emotional immaturity, often considered not ready to move on to the first grade of primary school. Teachers then advise that these children retain the last year of preschool. Grade retention in primary school occurs if children cannot keep up with peers. Children with severe learning impairments or problem behavior are referred to special educational services.

TABLE 1 Sample Characteristics of the Very Preterm and Term Group

	Groups					
	Very Preterm (*n* = 200)			Term (*n* = 230)		
Age[a], mean (SD), range, y	8.2	2.5	4.0-12.0	8.3	2.3	4.0-12.0
Gestational age, mean (SD), range, wk	28.1	1.4	24.5-30.0	39.9	1.2	37.0-43.0
<28 wk, *n* (%)	87.0	43.5		0.0	0.0	
Birthweight, mean (SD), range, g	1013.0	287.0	460-1900	3578.0	482.0	2500-5025
<1500 g, *n* (%)	191.0	95.5		0.0	0.0	
Boys, *n* (%)	106.0	53.0		106.0	46.1	
Estimated IQ[b]	93.3	15.8	70.0-138.0	105.0	13.4	70.0-141.0
Parental education[c], *n* (%)						
High	45.0	23.1		109.0	47.3	
Intermediate	75.0	38.2		79.0	34.3	
Low	80.0	38.7		33.0	14.3	
Minor neurosensory dysfunction, *n* (%)	37.0	18.5		13.0	5.6	
Minor vision loss or corrected with contact lenses or glasses	26.0	13.0		13.0	5.6	
Minor hearing loss or corrected with hearing aids	5.0	2.5		0.0	0.0	
Spastic unilateral cerebral palsy	6.0	3.0		0.0	0.0	

[a]Age of the very preterm children is not corrected for prematurity.
[b]IQ was estimated using the subtests Vocabulary and Block Design of the WISC-III,[19] or Wechsler Primary and Preschool Scale Intelligence-Revised (WPPSI-R)[52](depending on the child's age). Subtest scores were converted into a composite score that was used to calculate an estimated IQ, which correlates highly (0.9 range) with full-scale IQ.[53]
[c]Highest of two parents. Low = primary education only or prevocational secondary education; intermediate = 3-year secondary education or middle vocational education; high = higher professional, university training or PhD.

Preschool and Academic Achievement Measures

Preschool and academic achievement was assessed using a comprehensive series of standardized tests which are part of the Dutch National Pupil Monitoring System.[9] A vast majority (±95%) of the Dutch schools use this unique monitoring system for preschool and primary school pupils which enables teachers to monitor their pupils' development in relation to both individual and peer development, at given moments during a school year, and over time.[9] The system provides a schedule prescribing which tests should be performed at specific points in time during the first two preschool years and grade 1 to 6, i.e. beginning, middle, or end of the school year. Each derived raw test score is converted into an Ability score. The Ability scores collected throughout a school year reflect progression in performance, and if compared between grades they allow meaningful comparison of results across grades. To ensure measurement of progress in Ability scores on a single dimension (i.e. difficulty of the items and the latent ability can be represented on the same scale), a measurement technique based on item-response-theory (IRT) was used in constructing the monitoring system.[10] In the applied IRT model (i.e. One Parameter Logistic Model) the chance that an item can be solved successfully is specified as a function of a latent one-dimensional pupil ability and one or more item characteristics (e.g. item difficulty).[11,12]

Preschool assessment includes the Reasoning test[13] and the Early Linguistics test.[14] Alpha coefficients as a measure of reliability for both tests are higher than .81.[13,14] The Reasoning test measures numerical reasoning skills that require classifying, sorting, comparing, and counting of objects. The Early Linguistics test measures meta-linguistic skills, such as receptive language, phonological awareness, auditory synthesis, as well as sound and rhyme. Primary school tests include the Three Minutes Test, Reading Comprehension test, Spelling test, and Mathematics/Arithmetic test.[9] Alpha coefficients for these tests are higher than 0.88.[15-18] The Three Minutes Test (TMT)[17] measures fluency of word reading and comprises of three different cards that have to be read aloud by the child in one minute and which increase in difficulty and complexity. The TMT card 1 and 2 measure word reading of simple words and both contain 150 monosyllabic Consonant-Vocal words (e.g. bank) and are administered in grade 1 and 2. The TMT card 3 measures word reading of complex words and depicts 120 disyllabic words (e.g. autumn), which is administered in grade 3 and successive grades. The Reading Comprehension test[18] comprises series of different texts with accompanying multiple-choice questions for each text to be answered by the child. The Mathematics/Arithmetic test[15] assesses general knowledge of mathematics and arithmetic and comprises written computational problems of addition, subtraction, multiplication, and division, and problems regarding the notion of time and use of money. The Spelling test[16] requires writing down verbally presented words that increase in difficulty level. For all tests, the dependent variable used was the total number of correct responses (e.g. words written or problems solved). For more information on these tests please refer to www.cito.com.

The subtests Vocabulary and Block Design of the Wechsler Intelligence Scale for Children-III (WISC-III)[19], or Wechsler Primary and Preschool Scale Intelligence-Revised (WPPSI-R)[20] (depending on the child's age) were used to derive an estimated full-scale IQ. The estimated full-scale IQ correlates highly (0.9 range) with full-scale IQ.[21] Subtest scores were converted into a composite score that was used to calculate an estimated full-scale IQ.[22]

Procedure

The collection of the current data was embedded in a larger study into the neurobehavioral outcomes of very preterm children. Parents of all participating children provided written informed consent to participate in the study. Data on academic achievement were collected at the children's schools. Intelligence assessment and completion of the questionnaires of the very preterm sample took place at the Erasmus University Medical Centre Rotterdam Sophia Children's Hospital in Rotterdam. Comparison children were assessed at their schools. The medical ethics review board of the Erasmus University Medical Centre Rotterdam approved the study protocol.

Statistical Analyses

Univariate analyses of variance were used to analyze group differences between very preterm and comparison children for the preschool and academic test scores data while adjusting for parental education (highest of the two parents), gender, grade, and period of assessment. Interaction effects between group (very preterm versus comparison group), grade, and parental education were calculated, as well as the interaction effects between group and grade, and between group and parental education. Exploratory analyses examined differences in academic performance between very preterm children that retained a grade and those who did not. To determine the strength of effects, we calculated effect sizes in terms of Cohen's d. Cohen's guidelines were followed to indicate the strength of effect sizes, and effect sizes greater than 0.5 were considered a significant clinical effect.[23] For all analyses, a *P*-value of < 0.05 (two-tailed) was considered statistically significant.

RESULTS

Sample Differences

TABLE 1 presents information on sample characteristics for the very preterm ($n = 200$) and comparison group ($n = 230$). The very preterm group had a significantly lower gestational age ($F = 8643.9$, $p < 0.001$), lower birthweight ($F = 9381.2$, $p < 0.001$), lower mean IQ ($F = 111.5$, $p < 0.001$), lower mean level of parental education ($\chi^2 = 50.4$, $p < 0.001$), and more minor disabilities ($\chi^2 = 27.8$, $p < 0.001$) than the comparison group. There were no group differences for age at assessment ($F = 0.09$, $p = 0.8$), or gender ($\chi^2 = 1.1$, $p = 0.3$).

TABLE 2 lists the perinatal characteristics of very preterm children.

Rates of Grade Retention and Special Education

Twenty-four (12%) very preterm children attended special education, which included schools for children with learning difficulties and/or behavioral problems. In the Netherlands 4.8% of the children in this age range attend special schools. Significantly more very preterm children retained a grade: 51 (25.2%) versus 5 (2.3%) comparison children ($\chi^2 = 48.4$, $p < 0.001$), of which the majority (68%) retained the second year

TABLE 2 Perinatal Characteristics of the Very Preterm Children

Perinatal Characteristics	*n* (%)
Intra Uterine Growth Retardation	47 (23.3)
Caesarian Section	120 (60.0)
Preeclampsia	65 (32.5)
Patent Ductus Arteriosus	84 (42.0)
Septicaemia	109 (54.5)
Necrotizing Enterocolitis grade II / III	5 (2.5)
Respiratory Distress with the use of Surfactant	131 (65.5)
Retinopathy of Prematurity grade I / II / III	21/ 16/ 2 (10.5/ 8.0/ 1.0)
Intra Ventricular Hemorrhage grade I / II/ III/ IV	17/ 25/ 8/ 2 (8.5/ 12.5/ 4.0/ 1.0)
Oxygen Dependence at 6 weeks corrected age	11 (5.4)
Duration of Assisted Ventilation	
mean ± *SD* (range), days	9.1 ± 10.2 (0-62)
Duration of stay on Neonatal Intensive Care Unit	
mean ± *SD* (range), days	43 ± 36.8 (1-221)
Prenatal steroids (Celestone)	141 (70.5)
Postnatal steroids (Dexamethasone)	35 (17.3)
Dopram	62 (31.0)

Note. Intra Uterine Growth Retardation is defined as an SDS score of -2 SD below expectation for gestational age.[36] Septicaemia was defined as a positive blood culture. Necrotizing Enterocolitis was defined according to criteria given by Bell et al.[37] Respiratory Distress requiring assisted ventilation.

preschool (n = 34). Of all participating children born in July to September (n = 112), 18 (14.3%) very preterm children versus 2 (1.8%) comparison children were not ready to start primary education at 6 years of age, and retained in the last year in preschool (χ^2 = 28.9, $p < 0.001$). Exploratory analyses showed that very preterm children who had retained a grade (n = 51) scored neither higher nor lower on the academic achievement tests than their very preterm peers who were in an appropriate grade for age (n = 149; all Fs < 2.2, all ps > 0.1).

Preschool and Academic Skill Development

TABLE 3 presents the scores for both groups, and the statistical values for the main effects of group and interaction effects of group and grade. In preschool, very preterm children performed 0.7 SD lower than comparison children on numerical reasoning skills, and did not perform significantly lower in early linguistics. From the beginning of primary school, very preterm children scored 0.4 SD lower on simple word reading, 0.3 SD lower on complex word reading, and 0.6 SD lower on mathematics/arithmetic, than the comparison group. Very preterm children did not score significantly lower on spelling and reading comprehension. After controlling for IQ, differences between very preterm children and the comparison children for complex word reading and mathematics/

TABLE 3 Main Effects of Group and Effect Sizes in Terms of Cohen's *d* and Interaction Effects of Group and Grade for the Preschool and Academic Subjects

	Groups		Main Effects of Group			Interaction Effects Between Group and Grade	
	Very Preterm	Comparison					
	M ± *SD*	*M* ± *SD*	*F*	*p*	*d*	*F*	*p*
Preschool Subjects[a]							
Numerical Reasoning	49.7 ± 15.2	61.8 ± 14.7	5.4	.03	.7	<.001	.1
Early Linguistics	72.3 ± 11.1	78.1 ± 11.5	2.2	.1	.4	na[b]	na
Academic Subjects[c]							
TMT card 1	66.0 ± 21.9	72.5 ± 53.7	7.8	.006	.4	3.5	.009
TMT card 2	57.7 ± 24.8	66.3 ± 53.5	5.1	.03	.4	11.7	<.001
TMT card 3	58.9 ± 21.5	68.5 ± 19.6	5.7	.02	.3	1.9	.1
Reading							
Comprehension	38.6 ± 23.6	39.9 ± 17.2	.4	.5	.1	1.2	.3
Spelling	131.3 ± 15.3	133.1 ± 11.6	.6	.4	.1	1.3	.3
Mathematics/Arithmetic	79.5 ± 18.9	88.1 ± 15.8	22.1	<.001	.6	.9	.5

Note. Results are adjusted for parental education and gender.
[a]Preschool constitutes two school years.
[b]Not assessed in the first year of preschool.
[c]Academic subjects are assessed in primary school which comprises of six school years (grade 1 to 6).

arithmetic remained significant (Fs > 4.8, ps < 0.03), and for numerical reasoning skills became borderline significant ($F = 3.2$, $p = 0.06$).

Group and grade interacted significantly for the TMT cards 1 and 2. This indicates that very preterm children performed significantly poorer than comparison children on simple word reading in grade 1 ($F = 4.3$, $p = 0.04$), but not in the following grades 2 to 4 ($F = 0.07$, $p = 0.8$). There were no significant interaction effects between group and grade for the complex word reading, reading comprehension, spelling, and mathematics/arithmetic. Group, grade, and parental education did not interact significantly (Fs < 1.5, ps > 0.1), nor were there significant interaction effects between group and parental education (Fs < 2.3, ps > 0.09).

DISCUSSION

In our meta-analysis we showed that academic areas of weakness in very preterm children encompass reading, mathematics/arithmetic, and spelling.[2] Information on preschool skills in these children, however, was lacking, and it remained questioned whether very preterm children already perform poorer than peers at an early school age when they enter primary school or, as they grow older.

The present study shows that in preschool very preterm children do well in early linguistics, but have clinically significant deficits in numerical reasoning skills. In primary school, these children perform comparable to peers in spelling and reading comprehension, however perform significant poorer than peers in complex word reading, and had clinically significant deficits in mathematics/arithmetic. The mathematics/arithmetic and word reading deficits were already apparent at the beginning of primary school and could not be explained by very preterm children's lower IQ. Group differences between very preterm and comparison children for simple word reading disappeared after grade 2, suggesting catch-up with peers for this academic subject. The absence of group by grade interactions for complex word reading and mathematics/arithmetic indicate that the rate of learning of very preterm children is comparable to term-born children, and that if very preterm children fail on these subjects at the very beginning of primary school, they continue to lag behind peers throughout their primary school career.

Research has shown that academic difficulties may be related to gaps in preschool skills.[4,27] Mathematical abilities at primary school age find their origin in the mastery of preschool numerical reasoning skills, such as sorting or counting of objects.[5,28] The observed numerical reasoning difficulties in our very preterm preschoolers are likely to underlie the mathematical difficulties observed at later ages. Whether training on these pre-academic skills at an early age may prevent later mathematical problems should be subject of further study. Reading requires the mastery and joint use of multiple skills, including letter recognition, translation of letters into sounds, and determination of the meaning of a word. Together these abilities are required to read accurately and understand the text (reading comprehension). [27] In the development of these skills, pre-reading linguistic abilities, such as phonological awareness, play a central role.[4] Previous research has not addressed the question which of these skills are impaired in very preterm children. Tests employed in our study encompass preschool linguistic skills, reading comprehension, and fluency of word reading of simple and complex words. Very preterm preschoolers did not show poorer early linguistic skills, nor had reading comprehension deficits. These findings suggest that reading difficulties in very preterm children may not be related to deficient linguistic processes, or text comprehension, but may be traced back to a general slowing of processing speed.[29]

More than a quarter of our very preterm sample functioned in a grade below age level. This rate is consistent with previous reports.[30,31] Most of the very preterm children retained a grade in preschool, and the main reason for grade retention in these cases was that these very preterm children were born in July to September and were considered not ready to move on to primary school. The purpose of grade retention is that another year of maturity and exposure to the curriculum of the repeated grade will prepare the child to meet the academic and social demands of the next grade.[32] However, previous research on the effects of grade retention in normally developing children has shown that grade retention alone does not appear to benefit academic performance.[33] When comparing all very preterm children who retained a grade, i.e. were in a grade lower for age, to very preterm peers who functioned in an appropriate grade for age, we found no significant differences in academic performance between both groups. Though grade retention might be of benefit for these childrens' social functioning, the effects of this policy to improve their academic skills might be questioned. Rather than putting the children through an educational program with which they've already had trouble, educators should find a better way to teach the material.

This study has some limitations. [34] Although the comparison sample was recruited for the same schools as the very preterm children attended to control for educational environmental characteristics, the level of parental education was high in the comparison group, possible because highly educated parents are more willing to participate. Parental education may influence academic outcomes; however there were no interaction effects between group and parental education. Therefore, we statistically adjusted for group differences in level of parental education when calculating group differences in preschool and academic achievement. Another limitation is the lack of longitudinal data that would have enabled to use growth curve modeling techniques to compare the developmental trajectories per academic subject of very preterm children with those of the comparison sample. Nevertheless, the psychometric properties of the academic achievement tests employed allow for a comparison of performance from grade to grade over successive years.[8,9,11]

In conclusion, this is the first study reporting performance in preschool and academic skills in a large sample of very preterm children aged 4 to 12 years in comparison to that of a term-born comparison group. Very preterm children perform comparable to the comparison group in early linguistics, spelling, and reading comprehension, however, have clinically significant deficits in numerical reasoning skills and in mathematics/ arithmetic. In primary school, they show catch-up with peers in reading of simple words, though continue to lag behind peers in reading of complex words and mathematics/ arithmetic. Grade retention does not seem to improve their academic skills,[35] and further efforts to develop intervention techniques that may help very preterm children overcome their (pre-) academic weaknesses[35] is needed. Future research should focus on factors influencing academic achievement including underlying neurocognitive dysfunctions, perinatal and social risk factors, and their roles as mediators or moderators on the effects of preterm birth.

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Chapter 4

The profile of executive function in very preterm children at 4 to 12 years

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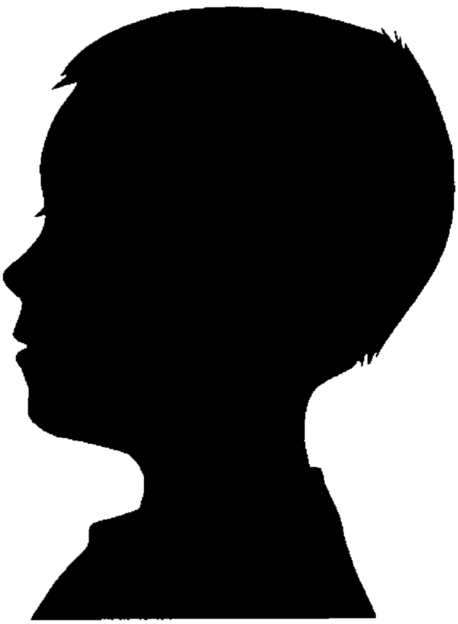

ABSTRACT

Objective

To examine executive functioning in very preterm (gestational age ≤ 30 weeks) children at 4.0 to 12.0 years of age.

Methods

Two-hundred very preterm (106 boys, 94 girls; mean gestational age 28.1 weeks, SD 1.4; mean age 8.2 years, SD 2.5) and 230 term children (106 boys, 124 girls; mean gestational age 39.9 weeks, SD 1.2; mean age 8.3 years, SD 2.3) without severe disabilities, born between 1996 and 2004, were assessed on an executive function battery comprising response inhibition, interference control, switching, verbal fluency, verbal and spatial working memory, and planning. Multiple regression analyses examined group differences while adjusting for effects of parental education, age, sex, and speed indices.

Results

Relative to term controls, very preterm children had significant ($p_s<0.02$) deficits in verbal fluency (0.5 SMD), response inhibition (0.4 SMD), planning (0.4 SMD), and verbal and spatial working memory (0.3 SMD), independent of slow and highly fluctuating processing speed. A significant group by age interaction indicated that group differences for response inhibition decreased between 4.0 and 12.0 years.

Conclusions

Very preterm birth is associated with a profile of affected and non-affected executive functions independent of impaired speed. Deficits are of small to moderate magnitude and persist over time, except for response inhibition for which very preterm children catch up with peers.

INTRODUCTION

Improvements in perinatal care have resulted in increased survival rates for children born very preterm (gestational age ≤ 30 weeks). The incidence of major disabilities, such as cerebral palsy (CP), intellectual disabilities, deafness or blindness, in these children is relatively low.[1] There is growing awareness, however, that a majority of the survivors with normal IQs is at risk for "subtle" neurocognitive deficits, such as motor impairments,[2] academic underachievement, and behavioral problems.[3]

Executive functioning (EF) has been considered to be one of the crucial mechanisms underlying academic and behavioral problems[4-8] and has therefore received much interest of research into very preterm children's outcomes the last decade. EF refers to interrelated neurocognitive processes, such as response inhibition, working memory, switching, planning, and fluency, that control thought and behavior. [8-10] Earlier studies have found EF deficits in very preterm children.[3,11] However, because of inclusion of often small numbers of children of restricted age ranges and the use of measures tapping into multiple aspects of EF, literature still diverges on which EF domains are precisely affected in this population and to what extent EF deficits persist over time.

Poor EF after very preterm birth has been related to smaller volumes of basal ganglia and cerebellum, as well as to disruptions of (sub) cortical white matter circuits connecting frontal, striatal, and thalamic regions. [12-13] These white matter disruptions affect efficiency of neural signaling which also result in slow processing speed and highly variable task performance (i.e. moment-to-moment fluctuations in speed).[14] It has, therefore, been postulated that poor EF in very preterm children may in fact reflect speed of information processing deficiencies.[15]

The aim of this study was to examine a comprehensive range of EF in a large sample of very preterm and term children across the age range of 4.0 to 12.0 years with well-defined and validated measures of EF. Response inhibition, interference control, verbal and spatial working memory, switching, verbal fluency, and planning, were assessed in a large sample of very preterm and term children who were comparable in age and sex. All children were free of major disabilities.

METHODS

Participants

The very preterm (gestational age ≤ 30 weeks) sample was derived from all (n = 706) very preterm surviving singletons admitted between 1996-2004 to the neonatal intensive care unit of the Erasmus University Medical Center, Sophia Children's Hospital Rotterdam, The Netherlands. For an elaborate description of the inclusion procedure and neonatal characteristics of very preterm children we refer to an earlier publication.[16] Briefly, twins were excluded as inclusion of these children would violate the assumption of independence of observations. Very preterm children with a severe disability (one that was likely to put the child in need of physical assistance to perform daily activities),[17] would not be able to perform tests as utilized in the present study and were therefore not invited. The present study was carried out in the years 2007 and 2008. The term control group was recruited from three regular primary schools located in the same neighborhoods as schools attended by the very preterm children and included children without histories of prematurity (gestational age > 37 weeks), perinatal complications, and neurological disorders.

Minor neurosensory dysfunctions as observed in participating children are presented in TABLE 1 and included (1) vision corrected to normal with contact lenses or glasses, (2) hearing loss corrected to normal with hearing aids, (3) spastic unilateral cerebral palsy, classified according to standards of the Surveillance of Cerebral Palsy in Europe (SCPE, 2000).

Measures

Response inhibition was measured with the Stop task that requires a child to respond as quickly and accurately as possible to a go-stimulus (cartoon airplane presented for 1000 ms) and to inhibit the response if a stop-stimulus (cross presented for 50 ms) is presented. The initial delay between the go-signal and stop-signal was 250 ms and was increased by 50 ms if the child inhibited the response, and decreased by 50 ms if the child did not succeed in inhibiting the response. Twenty-five percent of the trials were stop-trials. The intertrial-interval was 1500 ms. Two practice blocks of 24 trials of which the first included go-trials, and the second go-trials and stop-trials, preceded four experimental blocks of 48 trials of go-trials and stop-trials. Dependent variables derived included errors of commission and omission, and stop signal reaction time (SSRT),[18] an estimate of the time a child needed to stop his or her response (defined as mean reaction time (MRT) minus the mean delay).

TABLE 1 Sample Characteristics of the Very Preterm and Term Group

	Groups					
	Very Preterm (n = 200)			Term (n = 230)		
Age[a], mean (SD), range, y	8.2	2.5	4.0-12.0	8.3	2.3	4.0-12.0
Gestational age, mean (SD), range, wk	28.1	1.4	24.5-30.0	39.9	1.2	37.0-43.0
<28 wk, *n* (%)	87.0	43.5		0.0	0.0	
Birthweight, mean (SD), range, g	1013.0	287.0	460-1900	3578.0	482.0	2500-5025
<1500 g, *n* (%)	191.0	95.5		0.0	0.0	
Boys, *n* (%)	106.0	53.0		106.0	46.1	
Estimated IQ[b]	93.3	15.8	70.0-138.0	105.0	13.4	70.0-141.0
Parental education[c], *n* (%)						
High	45.0	23.1		109.0	47.3	
Intermediate	75.0	38.2		79.0	34.3	
Low	80.0	38.7		33.0	14.3	
Minor neurosensory dysfunction, *n* (%)	37.0	18.5		13.0	5.6	
Minor vision loss or corrected with contact lenses or glasses	26.0	13.0		13.0	5.6	
Minor hearing loss or corrected with hearing aids	5.0	2.5		0.0	0.0	
Spastic unilateral cerebral palsy	6.0	3.0		0.0	0.0	

[a]Age of the very preterm children is not corrected for prematurity.

[b]IQ was estimated using the subtests Vocabulary and Block Design of the WISC-III,[19] or Wechsler Primary and Preschool Scale Intelligence-Revised (WPPSI-R)[52](depending on the child's age). Subtest scores were converted into a composite score that was used to calculate an estimated IQ, which correlates highly (0.9 range) with full-scale IQ.[53]

[c]Highest of two parents. Low = primary education only or prevocational secondary education; intermediate = 3-year secondary education or middle vocational education; high = higher professional, university training or PhD.

Interference control was assessed using an Eriksen Flanker task[19] which involves neutral, congruent, and incongruent trials. A neutral trial consisted of a target arrow flanked by rectangles (==>== or ==<==), a congruent trial consisted of a target arrow flanked by arrows that pointed in the same direction as the target (>>>>> or <<<<<). An incongruent trial consisted of a target arrow flanked by arrows pointing in the opposite direction (incongruent) as the target (>><>> or <<><<), which causes interference.[19] Children were required to inhibit responses to these interfering stimuli. Stimuli disappeared after the child responded and were presented with a maximum duration of 3000 ms. The intertrial-interval was 1500 ms. A practice block of 12 trials (4 trials per type) preceded two experimental blocks, consisting of 36 trials each (24 trials per type). Incongruent trials induced slower reaction times and more omission and commission errors than congruent trials (p_s<0.001). Dependent variables were an interference score for MRT (i.e. MRT on incongruent trials minus MRT on congruent trials), and interference scores for errors of omission and commission.

Switching was measured using a stimulus-response compatibility task. Target stimuli, arrows, differed in color with a green arrow indicating that the child had to respond with a spatially compatible response (left arrow mapping onto left response button), and a red arrow indicating that the child had to respond with a spatially incompatible response (left arrow mapping onto right response button). Stimuli disappeared after the child responded and were presented with a maximum duration of 3000 ms. The intertrial-interval was 1500 ms. Two practice blocks of 6 trials each (6 compatible and 6 incompatible trials) preceded an experimental block consisting of 48 trials (24 compatible and 24 incompatible trials). Incompatible trials induced slower reaction times and more omission and commission errors than compatible trials (p_s<0.01). Dependent variables were a switch score for MRT (i.e. MRT on incompatible trials minus MRT on compatible trials), and switch scores for errors of commission and omission.

Spatial working memory was assessed using the Spatial Span (SSP) subtest of the Cambridge Neuropsychological Testing Automated Battery (CANTAB).[20] This test measures the capacity to temporarily store and manipulate spatial information. Children viewed a lighted sequence of squares and were required to reproduce the sequence by touching items on a touchscreen in the same order as originally illuminated. The dependent variable was the maximum span.

Verbal working memory was assessed using the backwards condition of the Digit Span subtest of the Wechsler Intelligence Scale for Children-III (WISC-III).[21] This test measures the capacity to temporarily store and manipulate verbal information. In the backwards condition, digits that were read by the examiner (one digit per second) were to be repeated in the reverse order. Children received one point for each correct response. The dependent variable was the total number of correct sequences.

Verbal fluency was measured in a task that required children to name as many examples of two specific categories: "animals" and "things you can eat or drink" within a 40-second time frame.[5] Two examples of each category were provided before the beginning of the task. An item named for the second time was scored as incorrect. The dependent variable was the total number of correct responses.

Planning was assessed using the CANTAB subtest Stockings of Cambridge (SOC).[20] The SOC is a touchscreen-adapted version of the Tower of London task. Children were instructed to solve problems by moving colored circles between three locations in a prescribed number of moves. Problems were graded in ascending difficulty, involving two to five moves required per problem. Dependent variables derived were number of problems solved, planning time, and execution time. Analyses were performed on trials with five moves taking performance on two-move trials into account to examine effects of increasing difficulty levels.

Processing speed was measured with the MRT on go-trials of the Stop task (only correct trials).

Fluctuations in speed were measured using the standard deviation of the MRT on go-trials of the Stop task divided by MRT (SD of MRT/MRT[22]).

IQ was estimated using the subtests Vocabulary and Block Design of the WISC-III,[21] or Wechsler Primary and Preschool Scale Intelligence-Revised (WPPSI-R)[23] (depending on the child's age). Subtest scores were converted into a composite score that was used to calculate an estimated IQ, which correlates highly (0.9 range) with full-scale IQ.[24]

Procedure

Assessments of EF and IQ for very preterm children took place at the Erasmus University Medical Centre Rotterdam, Sophia Children's Hospital Rotterdam. Control children were assessed at their schools. All assessments were performed by specifically trained experimenters using standardized instructions. Written informed consent was obtained from all parents of the participating children. The medical ethics review board of the Erasmus University Medical Centre Rotterdam approved the study protocol.

Statistical Analyses

Multiple linear regression analyses tested group differences between very preterm and control children for EF dependent variables. Raw scores were used in all analyses. Missing data were handled by casewise deletion. We examined assumptions of normality, linearity, and homoscedasticity, by visual inspection of the residual scatterplots.[25] For errors of commission and omission on the Stop task, and the Flanker task MRT interference score, the residual scatterplots deviated from a normal distribution due to heteroscedasticity. However, the widest spread in SDs of residuals was not greater than 3 times the most narrow spread.[25-26]

Parental education (highest of the two parents), sex, and age, may correlate with the EF measures[27-28] and were therefore entered as covariates in the analyses. Interaction effects with group were also inspected. Interaction effects with a significant R square change (ΔR^2) value that did not reach the threshold for a small effect (0.01)[29] were not interpreted. Analyses were conducted with and without adjustment for processing speed and fluctuations in speed, and IQ, and with and without inclusion of children with minor neurosensory dysfunctions. We calculated effect sizes in terms of standardized mean differences (SMD), which is the difference between two group means divided by an estimate of the within-group SD. Effect sizes of 0.2, 0.5, and 0.8, refer to small, medium, and large effects, respectively.[29] *P*-values <.05 (two-tailed) were considered significant. Analyses were performed with SPSS 17.0.

RESULTS

Sample Differences

TABLE 1 presents sample characteristics for the very preterm and term control group. Very preterm children had a significantly lower mean GA ($p<0.001$), lower mean BW ($p<0.001$), lower mean IQ (SMD = 0.80, $p<0.001$), lower mean level of parental education ($p<0.001$), and more minor neurosensory dysfunctions ($p<0.001$) than control children. There were no group differences for sex ($p = 0.29$), or age at assessment ($p = 0.81$). One-hundred-and-three children were 4 to 6 years of age, 79 children were 6 to 8 years of age, 107 children were 8 to 10 years of age, and 115 children were 10 to 12 years of age.

Group Differences in EF Task Performance

Missing data resulted from examiner error or child noncompliance and varied from 2% for the Verbal Fluency task to 12% for the Switch task. Hardware problems resulted in missing data for the Spatial Span (<18%) and for the Stockings of Cambridge (<7%). Error scores were analyzed for all participating children, however, for a number of children speed scores could not be interpreted reliably because of high error rates.[30]

TABLE 2 presents, per dependent variable, the number of children included in the analyses, the means and *SE*s for the very preterm and term control children, and group effects, in terms of unstandardized regression coefficients (*B*) and accompanying standard errors (*SE*).

There were no significant main effects of parental education. Main effects of sex were significant for the Stop task SSRT, omission and commission errors, and Stockings of Cambridge planning time ($t_s>2.28$, $p_s<0.01$), with girls outperforming boys in both the very preterm and term control group . There were no significant interactions between group and sex ($t_s<0.64$, $p_s>0.05$). Main effects of age were significant for all EF dependent variables ($t_s>2.54$, $p_s<0.02$), indicating better performance with increasing age. Age interacted with group for SSRT ($t = -2.37$, $p = 0.02$, $\Delta R^2 = 0.02$), showing a decrease of the group difference of 0.70 SMD, $p<0.001$ to 0.15 SMD, $p>0.12$, between 4 and 12 years of age.

TABLE 2 Means and *SE*s for the Very Preterm and Term-Born Children and Group Effects In Terms Of Unstandardized Regression Coefficients and Accompanying Standard Errors for the EF Dependent Variables

	Groups							
	Very Preterm			Control			Group Effects	
	n	*M*	*SE*	*n*	*M*	*SE*	*B*	*SE*
Response Inhibition								
Omission Errors	187	7.6	0.8	213	4.4	0.5	3.6***	0.8
Commission Errors	187	5.2	0.5	213	2.9	0.3	2.5***	0.5
Stop Signal Reaction Time	179	316.3	7.6	211	82.1	5.5	37.1***	8.5
Interference Control								
IS Omission Errors	184	0.8	0.2	219	0.3	0.1	0.5	0.2
IS Commission Errors	184	2.0	0.2	219	1.4	0.2	0.6	0.3
IS MRT	154	101.8	10.0	205	126.1	10.5	-1.5	13.6
Switching								
SS Omission Errors	189	0.3	0.2	224	0.8	0.1	0.1	0.1
SS Commission Errors	189	-0.6	0.4	224	-0.4	0.2	-0.1	0.4
SS MRT	138	11.1	8.9	197	29.5	6.8	-20.1	13.3
Verbal Fluency								
Total Correct	200	20.3	0.6	222	22.9	0.6	-2.9***	0.5
Verbal Working Memory								
Total Correct[a]	200	3.7	0.1	222	4.1	0.1	-0.5**	0.2
Spatial Working Memory								
Maximum Span	165	4.6	0.1	190	4.9	0.1	-0.4**	0.1
Planning								
Total Problems Solved	187	5.9	0.2	213	6.3	0.1	-0.5*	0.2
Planning Time	187	3765.0	299.3	213	4991.9	378.1	-131.2**	527.5
Execution Time	187	3083.4	413.7	213	3546.2	314.2	111.7	557.7

B, Unstandardized Regression Coefficient; IS, Interference Score; MRT, Mean Reaction Time; SE, Standard Error; SS, Switch Score.

[a]Backwards. *p<0.05, **p<0.01, ***p<0.001 (two-tailed).

Very preterm children had significantly poorer scores on the Stop task SSRT, omission and commission errors, on the Verbal Fluency total correct, Digit Span total correct sequences, Spatial Span maximum span, and Stockings of Cambridge planning time and problems solved (t_s>-2.72, p_s<0.007). Groups did not differ in Stockings of Cambridge execution time (t = 0.20, p = 0.84), Flanker task interference scores for MRT, errors of omission and errors of commission (t_s<1.68, p_s>0.10), and Switch task switch scores for MRT, errors of omission and errors of commission (t_s<-1.51, p_s>0.13).

Basic processing speed was significantly slower (0.40 SMD, t=5.06, p<0.001) and showed significantly greater fluctuations (0.70 SMD, t = 7.00, p<0.001) in very preterm children than in term controls. There were no interaction effects between group and these speed indices. Except for omission errors on the Stop task ($t = 1.56$, $p = 0.12$), group differences remained unchanged if processing speed and fluctuations in speed were taken into account. In the analyses with IQ, group differences for dependent variables of the Digit Span and Spatial Span, however, were no longer significant. Analyses with and without inclusion of children with neurosensory dysfunctions revealed similar results.

FIGURE 1 displays the SMDs for EF adjusted for covariates and speed indices, in a profile with the control group as the reference group (SMD = 0.0).

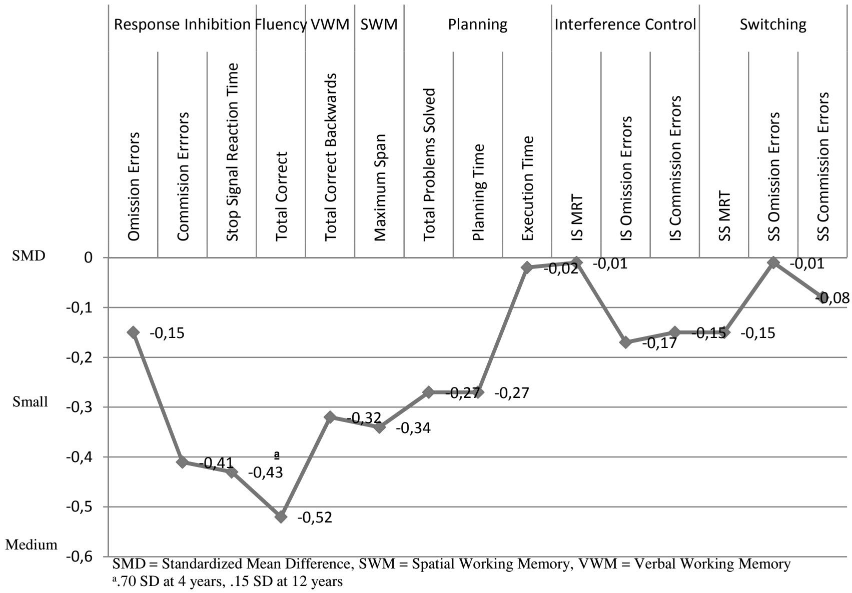

FIGURE 1 Profile of EF after adjustment for age, sex, and speed indices, with the term control group as the reference group (SMD = 0.0)

DISCUSSION

This study assessed EF in a large sample of very preterm and term control children aged 4.0 to 12.0 years in order to study how EF deficits in this sample are in the proportion of each other, whether these deficits are persistent over time, and their dependency on processing speed and fluctuations in speed.

The results show that, consistent with previous research,[3,11] very preterm children perform poorer than term children on EF measures with effect sizes ranging from small (0.3 SMD for working memory) to moderate (0.5 SMD for verbal fluency). Results add to our previous study on this issue[31] as well as to studies conducted by other researchers (for an overview please see[3,11]) in that we found that very preterm children catch up with peers in response inhibition, but stay behind in neurocognitive functions as fluency, planning, and working memory. In addition, we once more demonstrated that EF deficits cannot be explained by slow and highly fluctuating processing speed nor by lower IQ.[31] Results remained unchanged if very preterm children with neurosensory dysfunctions were excluded from the analyses.

Our very preterm sample did not perform poorer than controls on measures of interference control and stimulus-response switching. The results for interference control converge with earlier research showing that very preterm children do not perform slower and do not make more errors if faced with interfering information.[32-33] However, the results for switching contrast previous studies. For instance, across studies with very preterm children assessing switching with the Trail Making Test (TMT) Part B, a moderate effect size has been described, whereas we did not find a significant effect of very preterm birth.[3] However, differences between these studies and our results are likely due to differences in measures employed. The TMT part B, in contrast to our switch measure, heavily draws on visual-spatial abilities that are frequently observed to be impaired in very preterm children.[34-35] and thereby may bias switching effects. We also assessed inhibitory control as it has been considered the core deficit underlying attention disorders,[5] one of the major adverse outcomes of very preterm birth,[3] nevertheless only scarcely examined in this population. The Stop task allows measurement of the covert inhibitory process in the brain (i.e. stop signal reaction time) isolated from basic measures of information processing. Findings showed that, at early school age, very preterm children have significantly poorer inhibitory processes than same-aged term children, but that group differences between very preterm and term children disappear at middle school age. These findings suggest that poor inhibitory skills in very preterm children represent a maturational lag, although future research should replicate this finding.

The large sample size across the wide age range of 4.0 to 12.0 years included is not often seen in studies of executive functioning in very preterm children. Nevertheless, including four- and five-year-olds in such a study means assessing EF which have just began to emerge. A number of our preschoolers did not comply with task requirements or were impacted by difficulties with response buttons and touch-screen technology. However, more than two-thirds of the very preterm and control children were able to accomplish the tasks, which makes our findings on the progress of EF development in very preterm as compared to that in term children reliable.

A limitation was that, although term children were recruited from the same schools as attended by very preterm children to control for educational environmental characteristics, level of parental education was higher for term children than for very preterm children, possibly because highly educated parents are more willing to participate. Since there were no interactions between group and parental education, we adjusted for the influence of parental education by adjusted for parental education in the analyses. Another limitation was that assessments were done by experimenters who were not blinded to preterm birth status. However, the experimenters were specifically trained for the purposes of the study and used standardized instructions.

In conclusion, relative to term peers, very preterm children who are free of major disabilities and with IQs in the average range performed normal on interference control and switching measures, but performed poor on measures tapping into response inhibition, verbal and spatial working memory, verbal fluency, and planning; deficits that could not be explained by these children's slow and highly fluctuating processing speed nor by their lower IQ. Important 'take home' message is that executive dysfunction in these children is not a global deficit, but rather constitutes a unique profile of affected and non-affected areas which remains largely consistent between 4.0 and 12.0 years. It is the limited capacity or span to temporarily store and flexibly use information yet on top of slow and highly fluctuating speed that hinders these children and may cause a cascade of other neurocognitive deficits. For instance, the inattentiveness so frequently observed in very preterm children in classrooms,[3] or their lack of cognitive flexibility , may thus rather reflect their limited speed and stability to process and manipulate incoming stimuli than real interference control or switching problems. Applying the present results, clinicians and researchers working with very preterm children, may ensure that executive functions are tapped as 'purely' as possible and select EF tasks that are minimally dependent on other neurocognitive skills such as visual spatial skills or processing speed. In addition, employing IQ scores as an indicator of a child's neurocognitive functioning may not provide sufficient insight in the child's strengths and weaknesses.

The EF profile associated with very preterm birth as highlighted in this study supports remediation programs to be tailored to children of this population. These children's deficits in EF in addition to their slow and highly fluctuating response style may affect their academic achievement, as well as cause attention disorders, which is subject of our future research. Timely intervention, such as preschool program 'tools of mind',[36] trying to help very preterm children overcome their EF difficulties is necessary to prevent the onset of academic and behavioral problems.

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Chapter 5

Executive function in very preterm children at early school age

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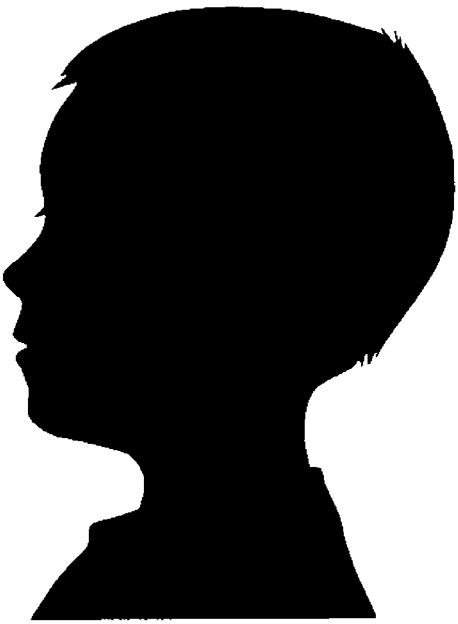

ABSTRACT

We examined whether very preterm (gestational age ≤ 30 weeks) children at early school age have impairments in executive function (EF) independent of IQ and processing speed, and whether demographic and neonatal risk factors were associated with EF impairments. A consecutive sample of 50 children (27 boys and 23 girls) born very preterm (mean age = 5.9 years, SD = 0.4, mean gestational age = 28.0 weeks, SD = 1.4) was compared to a sample of 50 age-matched full-term controls (23 girls and 27 boys, mean age = 6.0 years, SD = 0.6) with respect to performance on a comprehensive EF battery, assessing the domains of inhibition, working memory, switching, verbal fluency, and concept generation. The very preterm group demonstrated poor performance compared to the controls on all EF domains, even after partialing out the effects of IQ. Processing speed was marginally related to EF. Analyses with demographic and neonatal risk factors showed maternal education and gestational age to be related to EF. This study adds to the emerging body of literature showing that very preterm birth is associated with EF impairments.

INTRODUCTION

Better perinatal and neonatal care has improved survival rates for very preterm (gestational age ≤ 30 weeks) children. However, the developmental outcome of these children at later age is of significant concern.[1] Such outcomes include poor cognitive function, learning difficulties, and behavior problems such as Attention-Deficit/Hyperactivity Disorder (AD/HD),[2-4] which may result in school difficulties and the need for special assistance and special education.[5-6] Early identification of and better insight into these learning and behavioral problems would aid early intervention.

Executive function (EF) refers to a set of neurocognitive processes that are important for behavioral and cognitive regulation, and include inhibition, working memory, cognitive flexibility, goal selection, planning, and organization. Recent research has shown that learning difficulties and behavioral problems are both associated with deficits in executive function.[7-10] For example, deficits in inhibition, working memory and cognitive flexibility have been strongly associated with mathematical difficulties in children with a normal IQ.[11] Difficulties in reading and writing skills have been related to working memory and inhibitory control deficits.[12-15] Executive dysfunction has also been demonstrated in a range of behavioral problems.[8,16-17] Barkley (1997)[18] for example, has proposed that AD/HD arises from a deficit in inhibition, that in turn results in secondary EF deficits, such as impaired working memory.

A growing body of research is documenting that very preterm children show deficits in EF, including inhibitory control, working memory, verbal fluency, planning, switching or set-shifting, and attention (e.g.[19-30]). However, studies differ greatly in terms of their findings, measures employed, and age at assessment. Some studies have focused on isolated aspects of EF.[19] By employing a more comprehensive assessment, others demonstrated that executive dysfunction in very preterm children is a pervasive deficit that pertains to all domains of EF,[21-22] rather than comprising a pattern of strengths and weaknesses in EF. In terms of age groups, a range of researchers has examined EF in toddlers,[31-35] while others have focused on EF in very preterm young adults.[28,36-38] At early school age, which is the focus of the present study, some EF domains have been assessed extensively (e.g. inhibitory control), while others, such as cognitive flexibility and verbal fluency have received little attention. In addition, conceptual reasoning skills have not been examined at all in very preterm children at early school age. The present study was conducted to add to the limited literature targeting a broad range of EFs in very preterm children at early school age.

There is debate on the extent of overlap between the concepts of EF and IQ.[39] Some authors suggest that there is a substantial overlap,[40] others consider IQ and EF to be related yet distinct.[41-44] The extent of overlap may depend on the type of EF.[45] For example, set-shifting does not appear to be related to IQ,[42-43] while verbal fluency,[39] conceptual problem solving and cognitive efficiency, may be strongly related to IQ.[46] In addition, failure on IQ tests might be caused by impaired executive processes,[40] an issue only a few studies have addressed in very preterm children. In order to better understand the nature of the neurocognitive weaknesses that very preterm children encounter at early school age, it is necessary to disentangle the relationship of IQ and EF in these children.

Inhibitory control and switching tasks have been suggested to rely greatly on processing speed.[47-48] "Lower-order" cognitive processes, such as processing speed, have been proposed to underlie "higher-order" processes such as EF, [49-51] since white matter tracts are involved in processing information across different brain areas to establish various neuropsychological functions .[52] In very preterm children, white matter tract abnormalities have been reported,[53] which possibly result in slow speed of processing. Because a number of studies have reported slow speed of processing in very preterm children,[47,54-55] it has been questioned whether the EF deficits in very preterm children can be reduced to slower-than-average speed of processing.[55-56] So far, research has not examined the potential contribution made by slower processing speed to deficits in EF in very preterm children.

At last, our knowledge of the effect of demographic and neonatal risk factors on EF in very preterm children is limited. Knowing whether specific factors increase or rather decrease the impairments is essential for early intervention. While lower IQ scores and behavioral problems have been frequently associated with neonatal risk factors such as intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), chronic lung disease or sociodemographic disadvantage,[57-59] the unique contributions of demographic and neonatal risk factors to variations in EF in very preterm children remain unclear.

The primary aim of this study was to examine EF in a consecutive sample of very preterm children at early school age. We compared their performance on a comprehensive EF battery, assessing the domains inhibition, working memory, switching, verbal fluency and concept generation, to that of an age-matched, full-term control group. On the basis of the existing literature, we expected that the very preterm group would underperform the controls in all domains assessed. Our second aim was to explore whether deficits in EF (in particular inhibition and switching) could be explained by processing speed. Next, we examined group differences in EF while controlling for IQ and vice versa.

We hypothesized that the EF impairments in the very preterm group would remain existent after controlling for IQ. Finally, we examined the relationship between various demographic as well as neonatal risk factors and EF. It was hypothesized that a higher level of demographic and neonatal risk would be associated with poorer performance on the EF tasks.

METHODS

Participants

The study group consisted of 50 children born very preterm (i.e. gestational age ≤ 30 weeks, established by weeks and days after the mother's last menstrual period), and 50 controls. For the purposes of the current study, our very preterm sample was consecutively and randomly acquired from the total population of very preterm survivors (N = 276) born and admitted between 1998-1999 to the neonatal intensive care unit (NICU) of the Sophia Children's Hospital Rotterdam. Our sample did not differ from the total population of very preterm survivors in terms of gender, $\chi^2(1, 115) = 1.15$, $p = 0.30$; gestational age, $F(1, 113) = 1.16$, $p = 0.24$; birthweight, $F(1, 113) = 0.96$, $p = 0.33$; days of ventilation, $F(1, 113) = 0.04$, $p = 0.84$; days of added oxygen, $F(1, 113) = 0.34$, $p = 0.54$; or days of intensive care, $F(1, 113) = 0.28$, $p = 0.66$. The control group (mean gestational age = 39.7, SD = 1.3; mean birthweight = 3579, SD = 510) was recruited from local elementary schools as a part of a normative study of the VU University Amsterdam. Included in the control group were normally developing children without histories of prematurity (i.e. gestational age > 37 weeks), perinatal complications, psychiatric and neurological disorders. Exclusion criteria for both groups were mental and/or motor handicaps too profound to allow task execution. Written informed consent was obtained from all parents of the participating children. The study was approved by the Erasmus Medical Centre medical-ethical review board.

TABLE 1 presents the sample characteristics of the very preterm and the control group. No significant group differences were found for age, level of maternal education, or for the distribution of both genders. Very preterm children obtained lower IQ scores ($F(1, 98) = 20.2$, $p < 0.001$), and comprised of more twins and triplets ($\chi^2(1, 100) = 29.9$, $p < 0.001$), than the controls. Visual and hearing impairments were classified according to Wood et al.[60] Cerebral palsy was classified according to standards of the Surveillance of Cerebral Palsy in Europe (SCPE 2000). The SCPE standards (2000) differentiate between spastic (unilateral or bilateral), ataxic and dyskinetic (dystonic or choreo-athetotic) CP. Thirteen (26%) very preterm children had neurosensory impairments (eight with visual impairment, two with hearing impairment, one with cerebral palsy, and one with both

TABLE 1 Sample Characteristics of the Very Preterm and the Control Group

	Groups			
	Very Preterm		Control	
Age, mean y ± SD[a]	5.9	(0.4)	6.0	(0.6)
Level of maternal education, mean (*SD*)	3.9	(0.9)	4.2	(0.8)
IQ, mean (*SD*, range)	92.5	(17.5, 70-140)	109.0	(19.2, 71-150)***
Boys, *n* (%)	27	(54.0)	23	(46.0)
Twins or triplets, *n* (%)	11	(22.0)	0	(0.0)***
Visual impairment				
Impaired, use of glasses, *n* (%)	9	(18.0)	0	(0.0)***
Blind or perceives light only, *n* (%)	0	(0.0)	0	(0.0)
Hearing impairment				
Impaired, use of hearing aid, *n* (%)	2	(4.0)	0	(0.0)
Deafness, *n* (%)	0	(0.0)	0	(0.0)
Cerebral Palsy				
Spastic (unilateral), *n* (%)	3	(6.0)	0	(0.0)
Ataxic, *n* (%)	0	(0.0)	0	(0.0)
Dyskinetic, *n* (%)	0	(0.0)	0	(0.0)

Note. Level of maternal education: 1 and 2 = primary education/secondary education not finished; 3 = secondary education; 4 = intermediate vocational education; 5 = higher vocational education; 6 and 7 = university (Central Office of Statistics, 1992).
*p < .05.
**p < .01.
***p < .001.

cerebral palsy as well as with visual impairment). Visual and hearing impairments, and CP, are hereafter referred to as neurosensory impairments. Three (6%) very preterm children were formally diagnosed with Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), of whom two participated in special education. None of the children in the control group had neurosensory impairments.

TABLE 2 presents the neonatal characteristics of the very preterm group. The severity of neonatal illness is expressed in the Neurobiological Risk Score (NBRS) total score.[62] The NBRS total score is a composite measure of neonatal risk that summarizes neonatal medical events, with higher scores indicating higher degree of neurobiological risk.

Measures

Go/NoGo The Go/NoGo task is a well-established measure of inhibition with adequate psychometric properties.[64-66] In this study an adaptation of the original Go/NoGo paradigm was used[67] which has previously been employed. [68] Children completed a Go/NoGo task in which images of an elephant or a dog appeared on a computer screen. Children were instructed to respond to the elephant (Go-stimulus) and to withhold their response

TABLE 2 Neonatal Characteristics of the Very Preterm Group

Neonatal Characteristics	
Birthweight in grams, mean (*SD*, range)	1042.6 (31.8, 605.0-1640.0)
Gestational age in weeks, mean (*SD*, range)	28.0(1.4, 25.0-30.0)
Duration of NICU stay in days, mean (*SD*)	78.7 (22.9)
< 750 g birthweight, *n* (%)	3.0 (6.0)
< 28 weeks gestational age, *n* (%)	23.0 (46.0)
Outborn, *n* (%)	4.0 (8.0)
Assisted ventilation, *n* (%)	5.0 (84.0)
Grade I/II Intra ventricular hemorrhage, *n* (%)	11.0 (22.0)
Grade III/IV Intra ventricular hemorrhage, *n* (%)	0.0 (0.0)
Periventricular Leukomalacia, *n* (%)	2.0 (4.0)
Hypoglycemia, *n* (%)	0.0 (0.0)
Meningitis, *n* (%)	2.0 (4.0)
Necrotizing enterocolitis, *n* (%)	0.0 (0.0)
Chronic lung disease, *n* (%)	27.0 (54.0)
ROP (Grade I/II/III), *n* (%)	7.0/8.0/1.0 (14.0/16.0/2.0)
Small for gestational age, *n* (%)	3.0 (6.0)
Neurobiological risk score[a], mean (*SD*)	3.5 (.9)

Note. Outborn refers to infants born in community hospitals and referred to the perinatal center for neonatal intensive care. Chronic lung disease is defined as oxygen dependence at 36 weeks corrected age. Small for gestational age is defined as birthweight less than the 3rd percentile for gestational age (Usher and McLean, 1969).
[a]0-4 = Low. 5-7 = Medium. > 8 = High.

when the dog appeared (NoGo-stimulus). Each trial began with a 200 ms fixation cross on the screen. After a 300 ms delay, the Go- or NoGo-stimulus was presented for 1000 ms, with a fixed interstimulus interval of 1500 ms. A fixed interstimulus interval was used as variable intervals (specifically shorter ones) would have made the task too difficult for the youngest children. Fifty percent of trials were Go-trials, and the trials were shown in a random order. After an initial practice block of 12 stimuli, where the child was required to respond correctly to at least 5 consecutive stimuli in order to proceed to the experimental trials, an experimental block consisting of 24 stimuli was completed. The total number of correct responses and efficiency of responding (total number of correct responses divided by the mean reaction time of correct responses) was used as an index of inhibition. Measures of efficiency have been used in previous studies on EF performance in preschoolers.[69-70] Efficiency measures comprise both accuracy and response time and take into account Speed Accuracy Trade Off (SATO). As response time improves significantly during early childhood, the use of efficiency measures is valuable specifically in studies with young children.

The Shape School The original Shape School task is a storybook for preschoolers, designed to measure inhibition and switching processes.[70] Adequate psychometric properties have been established for the Shape School task.[71] In the current study, we used a computerized, modified version of the Shape School.[72] Children were asked to respond using response buttons (see Procedure for details regarding the response buttons). Children responded by pressing either the red or yellow button, depending on the color of the figure and the rule accompanying the condition. Three conditions were administered: the control, inhibition, and switching condition. In the control condition, the child was asked to respond to the color of the figures by pressing the corresponding button as quickly as possible. In the inhibition condition, children had to respond whenever they saw a figure with a happy face (fifty percent of the trials were inhibitory trials), but were instructed to suppress a response whenever they saw a figure with a sad face. In the switching condition, children had to give an opposite response (switch) by pressing the button that was originally linked with the other color whenever the figure was wearing a hat (fifty percent of the trials were switch trials). All conditions started with an initial practice block of 12 stimuli, where the child was required to respond correctly to at least 5 consecutive stimuli in order to proceed to the experimental trials, after which an experimental block consisting of 24 stimuli was completed. Trials were randomized within each condition. Stimuli were preceded by a 200 ms fixation cross and a 300 ms delay, and were presented for 2000 ms in condition A and B, and for 3000 ms in condition C, with a fixed interstimulus interval of 1500 ms. Dependent variables used in this study were: mean reaction time (RT) in ms on all trials from the control condition (measure for speed of processing); and the total number of correct responses and efficiency of responding (i.e. total number of correct responses divided by mean RT of correct responses) from the inhibition and switching conditions.

Day-Night task The Day-Night task is a well-validated measure of prepotent response inhibition in young children.[73-75] In the Day-Night task,[74] children were shown a set of 16 cards with pictures of either a sun or a moon with stars. There were two conditions: (1) a control condition, in which the child had to say "day" in response to a sun card and "night" in response to a moon card, and (2) an experimental condition, where the child was asked to respond to the sun card by saying "night" and vice versa. In both conditions, the same set of cards was used, shown in a pseudorandom order. Response time for each condition for the total of 16 cards was recorded manually using a stopwatch. The dependent variables used in this study were the total number of correct responses and the efficiency of responding in the control condition and experimental condition (i.e. total number of correct responses divided by the total naming time).

Verbal Fluency In this Verbal Fluency task ,[44] children were asked to name as many examples from two specific categories: "animals" and "things you can eat or drink" within a 40-second time frame. Two examples of each category were provided before the beginning of the task. An item named for the second time was scored as incorrect, as well as examples that fell outside above-mentioned categories. The total number of correct words across both categories was used as an index for verbal fluency.

Word Span This task, based on the Digit Span subtest of the Wechsler IQ Scale for Children[76] was used to assess verbal working memory.[67] A string of words was read aloud, and the child was asked to repeat the words. Similar to the WISC subtest, the number of words increased across trials, to a maximum of six words. There were two strings of words within each trial. The child had to repeat at least one string correctly in order to proceed to the next trial. In the forward condition, words had to be repeated in the same order as read by the examiner, and in the backward condition, words were to be repeated in the reverse order. The dependent variables used in this study were the total number of correctly recalled strings in the forward and backward condition, of which the latter served as an index for working memory.

Object Classification Task for Children (OCTC) The original Object Classification Task for Children[77] is a concept-shifting task that requires the child to group six toys according to three predetermined groupings: color (red or yellow), size (big or small), and function (car or plane). In this study, as opposed to toys, we used cards. These cards depicted yellow or red cars or planes, and could be sorted according to the same predetermined groupings as the toys in the original task. There were three conditions characterized by three increasing levels of structure in terms of help supplied by the examiner: (1) Free generation, where the child is required to sort the cards without any help of the examiner, (2) Identification, where the examiner constructs a category and the child is asked to identify the sort, and (3) Explicit cueing, where the child is explicitly told how to sort the cards. These different conditions will be explained below. First, there were two practice trials, where the child was asked to sort four cards depicting two different Disney figures (two cards showed identical pictures of Mickey Mouse, the other pair contained images of Donald Duck). The child was asked to "put the ones that are the same on this side of the table and the other ones that are the same on the other side of the table". These practice trials were designed to assess whether a child was able to sort according to overall appearance.

After these practice trials, the experimental trials started with presenting six cards to the child. In contrast to the practice trials, these cards did not show identical images that needed to be matched, but instead the child was required to sort the cards according to color (three cards showed red images, the other three cards displayed images in yellow), size (three cards depicted small images, the other three images were large), or function (three cards displayed cars, the other three had planes on them). The child was told, "there is something the same about these images", and was then asked to put the ones that are the same on this side of the table and the other ones that are the same on the other side of the table". After a correct sort of one of the three groupings (i.e. color, size or function), the child was encouraged to verbally name the identified grouping "So why did you place these cards on this side of the table and the other ones over there? What's the same about these pictures?". The child's answer was recorded and the examiner then mixed up the cards and asked the child to "make two groups again, but this time, something else has to be the same". This procedure was repeated until the child had correctly sorted the cards according to the three different groupings. For each correct sort, the child received 3 points. In addition, one point was given for each correct verbally named grouping. The maximum score which could be received was 12 points. If the child had arranged the cards correctly according to color, size or function, but was unable to sort the cards again for a second (or third) time, the examiner sorted the cards according to one of the remaining categories. The child was then asked to identify the sort ("So can you tell me what's the same about these cards?"). This is called the Identification condition. If the child answered correctly, a score of 2 points were given. If the child was unable to identify the sort, the examiner specifically asked the child to sort the cards according to a particular grouping ("Can you put all the red ones over there, and all the yellow ones over there?"). This was called the Explicit cueing condition, where the child received one point for each correct sort. However, if the child did not understand task instructions when first presented with the six cards, one dimension was removed, and the child was shown four cards, which could be sorted according to either color or size. Testing procedures and point scoring system were similar to those described for the six cards. The total raw score was calculated by summing all the points earned and was used as an indication of childrens' ability to shift between concepts.

Intelligence Four subtests of the Wechsler Primary and Preschool Scale Intelligence-Revised[78-79] were used to estimate full scale IQ: Picture Completion, Vocabulary, Block Design and Similarities. The Vocabulary and Similarities (Verbal Scale) subtest scores were added up, and then multiplied by three. The same procedure was followed for the Picture Completion and Block Design subtests (Performance Scale). Both the Verbal and Performance Scale scores were then added up into a composite score, of which the corresponding full scale IQ could be derived from the manual.[80] Scores on these subtests correlate highly (0.90 range) with full scale IQ.[81]

Procedure

Specifically trained experimenters administered all measures using standardized instructions. To control for order effects, measures were administered in two different orders. Half of the children in each group performed the tasks according to order A (Intelligence subtests - Day-Night task - Go/NoGo - OCTC - Shape School control condition and inhibition condition - Verbal Fluency - Shape School switching condition - Word Span), while the other half of the children of in each group performed the tests according to order B (Intelligence subtests - Go/NoGo - Word Span - Shape School control condition and inhibition condition - Verbal Fluency - Shape School switching condition - OCTC - Day-Night task). Computerized tasks were administered using the E-Prime software package (Psychology Software Tools, Pittsburgh, PA) and a Dell Latitude D800 laptop with a 15.4-inch color screen. Two response buttons were placed right in front of the laptop. Children responded by making a button press with one hand, but were required to keep both hands placed on top of the buttons so that they could react as quickly as possible. The buttons were converted emergency stop switches, with an external diameter of 94 mm (MOELLER Safety Products; model number: FAK-R/V/KC11/1Y). The stimuli were 700 pixels high and 500 pixels in width and presented with a 45º visual angle. Total duration of testing was ninety minutes, and frequent breaks were introduced to avoid fatigue. The children were examined individually in a quiet room while one of their parents was present.

Statistical Analyses

The observations in this study were not strictly independent, given the large number of multiple births. Therefore, we applied the method of mixed modeling, i.e. random regression modeling (RRM), to take the relatedness of the multiple births into account. The error structure was assumed to be related (compound symmetry) which implies that both correlations and variances within the multiple births did not differ significantly.

Group differences for the EF task dependent variables were analyzed with group (very preterm versus control) as the between subjects factor. We also examined group differences both with and without controlling for maternal education, and both with and without inclusion of the subset of very preterm children with neurosensory impairments. Chi-square statistics were carried out to determine if there were group differences in rates of EF impairments. An impairment in EF was defined by a mean score on the EF dependent variable greater than one SD below the control group mean.[30]

To examine the task specific impact of baseline processing speed, analyses were run while controlling for mean RT on the control condition of each specific task. Thus, group differences in performance on the Go/NoGo task and the Shape School inhibition and switching conditions (both tasks parallel in main task characteristics) were reanalyzed while entering the mean RT on the Shape School control condition as a covariate. Similar analyses were performed for the Day-Night task experimental condition, with mean RT on the Day-Night task control condition serving as a covariate.

Pearson's correlation coefficients were calculated for the relationship between IQ and the EF dependent variables. Cohen's guidelines were followed to indicate the strength of the correlation coefficients, with 0.10, 0.30, and 0.50 referring to small, medium, and large coefficients, respectively.[82]

Next, group differences in EF were reanalyzed with IQ as a covariate, and vice versa. In addition, effect sizes in terms of Cohen's d are provided. Cohen's guidelines were followed to indicate the strength of effect sizes, with 0.20, 0.50, and 0.80 referring to small, medium, and large effect sizes, respectively.[82]

Hierarchical, multiple regression analyses were conducted to test the impact of demographic and neonatal variables on the EF dependent variables of the very preterm group. The demographic predictor variables gender and maternal education were entered in the first block, gestational age in the next block to examine the impact of gestational age over and above background demographics, and finally the NBRS total score as an index of neonatal illness was entered in the last block. For all analyses, the threshold for significance was set at $p < 0.05$ (two-sided).

Missing Data and Extreme Values

Missing data resulted from either examiner error or child noncompliance and was less than 4% for each of the dependent variables. Due to not pressing the response button hard enough, the percentage of missing data for the dependent variables of the Go/NoGo task was 9%. Missing data was replaced by means of Expectation Maximization.[83] Analyses with and without replaced missing data revealed similar results. Extreme values were defined as having an absolute z-score exceeding 3 SD_s from the group mean and identified in both groups separately. If an extreme value occurred due to examiner error (n = 1), the case was removed from the analyses. If due to child non-compliance (n = 1), the extreme value was truncated to either 0.5 SD beyond the next most extreme score if that score was $z < 3.0$.[84] Extreme values due to either excellent or poor test performance remained unchanged.

RESULTS

Convergent and Divergent Validity Coefficients

The convergent validity coefficient for the two measures of processing speed in the current study (mean RT on the Shape School control condition and mean RT on the Day-Night task control condition) was 0.45, $p < 0.01$. Convergent validity coefficients between the inhibitory control tasks ranged from 0.22 to 0.58, all *p*s < 0.001. For each of the other measured EF domains, i.e. working memory, switching, verbal fluency and concept generation, we have employed one task per domain. Therefore, convergent validity coefficients could not be calculated for these measures. Divergent validity coefficients between the EF measures employed ranged from 0.15 to 0.39, all *p*s < 0.001 (details are available from first author).

EF Task Performance

All participating children met the performance criteria for continuing on to the experimental trials during the practice phases of the Go/GoNo task and the Shape School task. TABLE 3 shows the means and standard deviations, and the statistical values indicating whether group differences were significant for the EF dependent variables. The very preterm group performed significantly poorer than the controls on all EF measures, except for the total number of correct responses and efficiency on the Shape School inhibition condition, or for total correct for the Word Span forward, for which group differences were nonsignificant. Controlling for maternal education did not alter these findings. Analyses with and without inclusion of the subset of very preterm children with neurosensory impairments, or with and without inclusion of the three very preterm children with PDD-NOS revealed similar results.[1]

TABLE 4 depicts the rates of EF impairments in the very preterm group and control group. In comparison to the control group, very preterm children exhibited significant impairments in all measured EFs, except for the Shape School inhibition condition, or Verbal Fluency for which group differences in impairment rates were not significant, all $\chi^2(1, N = 100) < 2.10$, $p > 0.05$.

Speed of Processing and IQ

To determine the impact of baseline processing speed on the results, we reanalyzed group differences for efficiency on the Go/NoGo task and the Shape School inhibition and switching conditions while covarying for mean RT on the Shape School control condition (as a baseline measure of processing speed). TABLE 3 presents the results of these analyses. Group differences for the Go/NoGo task remained significant after taking into account processing speed. Group differences for the Shape School switching condition,

TABLE 3 Means and Standard Deviations of the Dependent Variables, and Statistical Values Indicating Group Differences between the Very Preterm and the Control Group

								After Controlling for			After Controlling for		
	Very Preterm		Control		Group			Processing Speed[a]			IQ		
	M	*SD*	*M*	*SD*	F^b	*P*	*d*	F^b	*P*	*d*	F^b	*P*	*d*
SS Control time in ms	908.00	254.00	753.00	167.00	13.54	<.01	.74	-	-	-	9.06	<.01	.61
SS Inhibition total correct	21.30	.63	22.54	.22	2.36	.15	.31	.94	.35	.20	.57	.46	.15
SS Inhibition efficiency	.02	.01	.02	.01	.73	.41	.17	2.87	.11	.34	2.38	.15	.31
SS Switching total correct	18.84	.73	22.22	.28	7.66	.02	.56	3.15	.10	.13	1.83	.20	.27
SS Switching efficiency	.01	<.01	.02	<.01	4.29	.04	.42	.04	.84	.04	.00	.97	.01
Go/NoGo total correct	20.80	.57	22.60	.39	7.98	.02	.57	4.62	<.05	.19	3.24	.09	.36
Go/NoGo efficiency	.03	.01	.04	.01	16.92	<.01	.83	5.32	.04	.47	6.28	.03	.51
DN Exp total correct	13.15	.37	14.40	.23	7.40	.02	.55	1.04	.33	.21	.86	.37	.19
DN Exp efficiency	.41	.10	.62	.20	44.88	<.001	1.35	18.85	<.01	.88	15.26	<.01	.79
VF total correct	11.87	3.71	14.90	5.21	10.86	<.01	.67	-	-	-	5.40	.02	.47
WS total correct forwards	5.30	.23	5.84	.17	3.77	.07	.39	-	-	-	.97	.34	.20
WS total correct backwards	.90	.69	2.76	.87	15.61	<.01	.80	-	-	-	6.90	.02	.53
OCTC total points	7.32	2.10	8.80	2.01	14.69	<.01	.77	-	-	-	4.78	.04	.40

Note. DN Exp = Day-Night task experimental condition, OCTC = Object Classification Task for Children, SS Control = Shape School control condition, SS Inhibition = Shape School inhibition condition, SS Switching = Shape School switching condition, VF = Verbal Fluency, WS = Word Span.

[a]Processing speed is measured by the mean RT on the Shape School control condition.

[b]df = 1, 98.

[c]df = 1, 97.

TABLE 4 Rates of Executive Function Impairments in the Very Preterm and Control Group

Dependent variables	*n* (%)	*n* (%)	χ^2
SS Control time in ms	23 (46)	7 (14)	12.90***
SS Inhibition total correct	14 (28)	12 (24)	.21
SS Inhibition efficiency	0 (0)	2 (4)	2.04
SS Switching total correct	19 (38)	8 (16)	6.14**
SS Switching efficiency	12 (24)	3 (6)	6.35*
Go/NoGo total correct	11 (22)	4 (8)	3.84*
Go/NoGo efficiency	18 (26)	6 (12)	7.90***
DN Exp total correct	31 (62)	21 (42)	4.01*
DN Exp efficiency	33 (66)	10 (20)	21.58***
VF total correct	12 (24)	8 (16)	1.00
WS total correct forwards	23 (46)	19 (38)	.66
WS total correct backwards	18 (36)	1 (2)	18.78***
OCTC total points	18 (36)	5 (10)	9.54**

Note. Definition of an impairment is given in the text.
DN Exp = Day-Night task experimental condition, OCTC = Object Classification Task for Children, SS Control = Shape School control condition, SS Inhibition = Shape School inhibition condition, SS Switching = Shape School switching condition, VF = Verbal Fluency, WS = Word Span.
$^*p < .05$.
$^{**}p < .01$.
$^{***}p < .001$.

however, became nonsignificant after covarying for processing speed. Group differences for efficiency on the Day-Night task experimental condition were adjusted for mean RT on the Day-Night task control condition. Group differences remained significant.

Next, we examined the impact of IQ. Correlation coefficients between IQ and the EF dependent variables ranged from 0.13 to 0.46. Strong, nearly large[82] correlation coefficients were found for Word Span backwards ($r = 0.43$, $p < 0.01$), OCTC total points ($r = 0.44$, $p < 0.001$), and efficiency on the Day-Night task experimental condition ($r = 0.46$, $p < 0.001$). The majority of the EF group differences remained significant after controlling for IQ, except for the Shape School inhibition and switching conditions, for which group differences became nonsignificant. TABLE 3 presents the results of these analyses. Additional, exploratory analyses were conducted to examine whether group differences in IQ between the very preterm children and the controls persisted while controlling for EF. For the purpose of this analysis, we extracted a composite EF factor from eight EF dependent variables (i.e. total number of correct responses for each task) using Principal Components Analysis. One variable of each task was chosen to prevent an artificial clustering of variables from the same task. An unrotated covariance matrix revealed one factor with an eigenvalue greater than 1, which explained 49% of the variance. The factor loadings of the EF dependent variables ranged between 0.38 and 0.90. Group differences for IQ remained significant after entering the EF factor as covariate, $F(1, 97) = 12.04$, $p < 0.001$.

The Impact of Demographic and Neonatal Risk Factors on EF

Of the demographic factors gender and maternal education, which were entered in the first block, gender was not associated with any of the EF dependent variables. Maternal education explained 12% of the variance ($R^2 = 0.12$; $F(2, 47) = 3.26$, $p < 0.05$) in efficiency on the Shape School inhibition condition ($\beta = 0.31$, $p < 0.05$), and did not predict performance on any of the other EF dependent variables (variance explained ≤ 4%, all *p*s > 0.25). Gestational age, entered in the second block, explained 12% of the variance ($R^2 = 0.08$; $F(1, 46) = 4.12$, $p < 0.05$) in performance on the OCTC ($\beta = 0.29$, $p < 0.05$), however was not predictive for the other EF dependent variables, (variance explained < 6%, all *p*s > 0.09). The NBRS total score, which was entered in the third or final block, did not predict performance on any of the EF measures (variance explained ≤ 7%, all *p*s > 0.08).

DISCUSSION

This study compared test performance of 50 very preterm children at early school age to that of 50 age-matched controls on a comprehensive EF battery. The findings demonstrated that very preterm children with average IQ performed significantly poorer than the healthy term born children on EF tests of inhibition, switching, working memory, verbal fluency, and concept generation. Group differences were not attributable to maternal education, and remained significant when very preterm children with neurosensory impairments were excluded from the analyses. In addition, very preterm children displayed significant higher rates of impairments in processing speed, inhibition, switching, working memory, and concept generation, than the controls.

We examined the impact of processing speed on inhibition and switching. Very preterm children demonstrated poorer inhibitory control than the controls on the Go/NoGo task and the Day-Night task. Group differences remained significant after controlling for processing speed, which suggests that very preterm children exhibit a deficit in inhibitory control in addition to slower processing speed. These findings converge with the findings of Christ et al.[47] Group differences for switching, however, became nonsignificant after covarying for processing speed, which suggests that switching difficulties in very preterm children might be explained by slow processing speed. Different cognitive processes are involved in switching, i.e. holding the switching rule in mind (working memory), inhibiting the incorrect response (inhibition), and switching response set.[73] The developmental pathways of these processes differ, and inhibition is one of the first EFs to emerge.[18,85] At early school age switching is still immature.[86] Performing immature cognitive processes heavily appeals to speed,[70] and as response time improves significantly during childhood[70] it seems that our results point to the fact that switching processes in very preterm children are so immature that these childrens' performance in switching tasks is dominated by processing speed.

The very preterm group obtained a mean IQ within the average range, which however was significantly lower than the mean IQ of the control group. It should be noted that the high average mean IQ of the control group might be associated with the high level of maternal education, though the groups did not differ significantly in level of maternal education. Group differences between the very preterm children and the controls could not be explained by differences in IQ. Our results are in line with research stating that EF is related to, yet distinct from IQ.[43] Among studies into EF in very preterm children, there is substantial variation in whether poor EF in these children is independent of IQ (e.g.[20,22,25,87]). Divergent findings across these studies might be related to differences in measures employed. For example, abbreviated IQ measures may not be as reliable as more comprehensive IQ measures, as extreme scores have far greater influence. In addition, some IQ measures have a greater focus on fluid intelligence in contrast to crystallized intelligence, than others, which is likely to result in higher correlations with EF.[88] In our study three of the four subtests employed to estimate IQ had a fluid component (Similarities, Picture Arrangement and Block Design). IQ is suggested to mostly influence more complex functions that require a greater degree of conceptual problem-solving ability and higher levels of cognitive efficiency,[46,88] which was supported by our findings showing a substantial overlap between IQ and measures of concept generation (OCTC), working memory, and (verbal) inhibition (Word Span backwards, and Day-Night task). In conclusion, to obtain a thorough understanding of very preterm childrens' neurocognitive difficulties, both EF and IQ should be measured, since EF and IQ are related yet distinct concepts.

In the present study, we investigated the relationship between demographic and neonatal risk factors and EF. We found that gender was not associated with EF. Although some studies with normally developing children found gender differences in performance on EF tasks,[89] most research agrees on that boys and girls show similar development of EF (e.g.[44]). In line with previous research [90] maternal education was, though marginally, associated with EF. This finding suggests a modest role for stimulating environmental aspects to improve EF, though more specific environmental factors, such as family functioning, parenting style, and the presence of resources and opportunities, might even have a greater contribution.[91] However, these factors were not targeted in the present study, and our sample size limited the inclusion of more than 5 predictors in the analyses. Creating a stimulating environment yet early in development should focus on parent instruction to enhance parent-child interaction.[91-92] Other environmental focused intervention techniques that have been shown to be successful in children with executive dysfunction include computer guided behavioral training.[93-95]

In our study, the degree of neonatal illness was not associated with poor performance on the EF tasks, although previously was demonstrated that a high level of neonatal illness was associated with poor working memory.[56] Our findings might be related to the fact that in our study the incidence of neonatal medical events such as infections or IVH was fairly low. Paralleling previous findings[28,36] we did find that gestational age was related to EF, in particular to concept generation. It might not be neonatal illness associated with preterm birth in particular that results in deficits in EF, but rather the preterm birth itself that constitutes the risk for EF deficits.[36]

Strengths of the study concern the sample, which comprises consecutive admissions, comparison to an age-matched control group, assessment at early school age, and statistical control for both IQ and speed of processing in the analyses. A limitation is that reliability and validity of our battery of neurocognitive measures have not been fully assessed for all measures. However, the use of experimental measures tapping into a comprehensive range of EF abilities with differing levels of complexity helps to chart the nature of the neurocognitive difficulties in very preterm children under various levels of executive demand. Some of our tasks have been specifically developed to capture neurocognitive processes underlying task performance.[71] In addition, verbal fluency and Go/NoGo tasks, as employed in the present study, have been found fruitful in elucidating functioning of the corpus callosum, cerebellum, cingulate gyrus, and prefrontal cortex in very preterm children and adolescents.[26,96-98] Future studies, using techniques such as functional imaging (fMRI) or diffusion tensor imaging (DTI), should be conducted to cast more light on how EF deficits in these children are related to white and grey matter pathology.

In conclusion, our findings add to the relatively small but rapidly growing literature on early school-aged very preterm children, and demonstrate poor performance on EF measures related to very preterm birth, which could not be explained by IQ. Furthermore, it shows that speed of processing is marginally related to EF in very preterm children. The results show that very preterm children are at high risk for EF impairments, beside the risk for adverse outcome at later ages already constituted by lower IQ scores and slow speed of processing.[99] An unresolved issue is whether EF deficits in very preterm children reflect a maturational lag or a permanent impairment. This question calls for a longitudinal approach. Nevertheless, the EF deficits observed may have important implications for their later academic and behavioral functioning.[8,11,100] Many follow-up studies document the outcomes of very preterm children in terms of neurosensory handicaps and IQ scores. However, of significant concern is the 'trend of worsening outcome' in the 'non-disabled' very preterm survivors.[1] An important role in this issue may be played by subtle deficits in cognitive processes such as EF which hamper the ability to function in an increasingly complex and demanding environment.[101] Our findings underline the need in neonatal follow-up care to extend the regular use of IQ assessments with the assessments of EFs and processing speed.

Footnotes

[1]Full results are available from the first author upon request.

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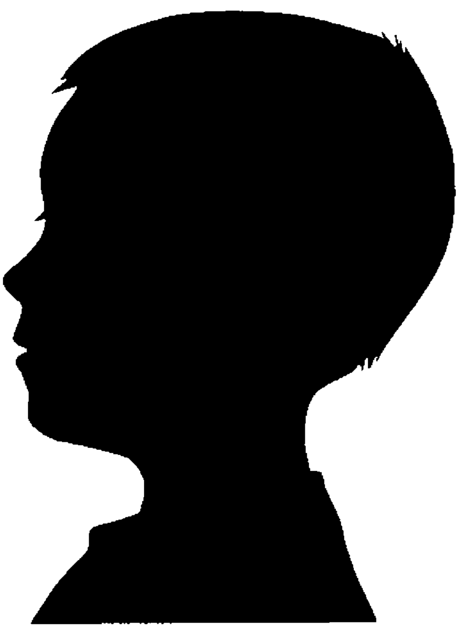
Chapter 6

Neonatal and social environmental predictors of executive function in very preterm children

Submitted



ABSTRACT

Objective

Very preterm children are at high risk for impaired executive function. Objective of this study was to examine associations between neonatal and parental education and executive function in very preterm (gestational age ≤ 30 weeks) children aged 4.0 to 12.0 years.

Methods

Two-hundred very preterm (mean age 8.2 ± 2.5 years) children and 230 term children (mean age 8.3 ± 2.3 years) without severe disabilities, born between 1996 and 2004, were assessed with measures of executive function including working memory, verbal fluency, planning, and inhibitory control. Neonatal risk factors (i.e. gestational age, birth weight standard deviation score, postnatal growth at six weeks corrected age, intra ventricular hemorrhage grade III and IV, oxygen dependency at 36 weeks postconceptional age, and meningitis and necrotizing enterocolitis) were obtained from clinical records. Parental education was derived from questionnaires. Multiple linear regression analyses identified associations between neonatal risk factors, parental education, and executive function in very preterm children while adjusting for gender and age.

Results

Very preterm children had significantly lower executive function scores (> 0.44 SMD, $p_s < 0.001$) than term children. A lower degree of dysmaturity (i.e. birth weight standard deviation score) was significantly ($\beta = 0.16$) related to better verbal working memory/fluency performance. Other neonatal risk factors were not significantly associated with executive function. Verbal working memory/fluency, spatial working memory/planning performance, and inhibitory control, were positively associated with parental education.

Conclusion

Executive function in very preterm children is associated with prenatal growth and level of parental education but not with neonatal complications.

INTRODUCTION

Very preterm (gestational age ≤ 30 weeks) children who survive without severe disabilities are at risk for a range of neurodevelopmental impairments.[1] One of the areas of neurodevelopmental functioning that attracts much interest of researchers the last decade is executive function since it has been demonstrated to be more important for school readiness than IQ.[2] Furthermore, executive function predicts academic success and behavioral regulation in very preterm children.[3-9] Executive function covers a set of neurocognitive functions including working memory, fluency, planning, and inhibitory control.[10-12] A substantial body of research shows that very preterm children have impaired executive function persisting at least into young adulthood.[13-16]

Contrasting to the amount of literature on differences in executive function between very preterm and term children, our understanding of neonatal risk and parental education associated with impaired executive function in this population is limited. TABLE 1 provides an overview of studies published between 1999 and 2011 that found significant ($p < 0.05$) associations between neonatal and/or parental education on the one hand and executive function on the other hand in children born very preterm (mean gestational age ≤ 30 weeks). Studies that did not find significant associations between these factors and executive function in very preterm children are not shown in this table. There is great variability in the published results because of diverging numbers of participants and substantial variations in measures used and children's age at assessment. In addition, effects of age have not been examined, although reported relationships may vary with age. Neonatal or biomedical factors may, for instance, be more influential in early development, whereas parental education may become more important as children grow older.

Objective of this study was to examine the predictive value of neonatal risk and parental education for impaired executive function in a large sample of very preterm children aged 4.0 to 12.0 years who were free of severe disabilities and to examine whether these influences vary with age or sex.

METHODS

Participants

The sample of 200 very preterm (gestational age ≤ 30 weeks) children was derived from all (n = 706) very preterm surviving singletons admitted between 1996-2004 to the neonatal intensive care unit of the Erasmus University Medical Center, Sophia Children's Hospital

TABLE 1 Overview of Previous Studies Reporting Significant ($p < 0.05$) Associations Between Executive Function, Neonatal Risk Factors and Parental Education in Very Preterm Children

Studies		Participants			Executive function measures		Significant ($p < 0.05$) associations reported
First author	Year	*n*	GA *M* (*SD*)	Age *M*	Name measure	Skill measured	
Ford	2011	45	26.4 (1.9)	7-9	Stroop	Interference control	Birth weight: β = .36, SES × Neurobiological risk[a]: β = .41
					Controlled Word Association Test	Verbal fluency	SES × Neurobiological risk[a]: β = .36
					Digit Span	Working memory	SES × Neurobiological risk[a]: β = .42
Woodward	2011	110	27.9 (2.3)	4.0	Tower of Hanoi	Planning	White matter abnormality at term: β = -.34
Luu	2011	337	28.0 (2.0)	16.1	D-KEFS Phonological Fluency	Verbal fluency	Severe brain injury: β = -3.6, parental education: β = .4
					D-KEFS Semantic Fluency	Verbal fluency	Severe brain injury: β = -3.9, parental education: β = .2
					D-KEFS Verbal Inhibition	Inhibitory control	Severe brain injury: β = -3.6, parental education: β = .3
					D-KEFS Cognitive Flexibility	Cognitive flexibility	Severe brain injury: β = -4.2, parental education: β = .3
					D-KEFS Spatial Planning	Planning	Severe brain injury: β = -4.0, parental education: β = .2
					D-KEFS Working Memory	Working memory	Severe brain injury: β = -3.9, parental education: β = .5
Aarnoudse-Moens	2009	50	28.0 (1.4)	5.9	Object Classification Task	Conceptual reasoning	Parental education: β = .31
					Go/NoGo	Inhibitory control	Gestational age: β = .29
Sun	2009	37	28.0 (1.9)	.7	A-not-B	Working memory	Low and high medical risk preterm < term
Taylor	2006	204	26.4 (2.0)	8.7	NEPSY		Ultrasound abnormality: β = -1.0
							<750 g birth weight: β = -.9
							Necrotizing enterocolitis: β = -2.3
							Postnatal steroid therapy: β = -1.0
Luciana	1999	40	30.3 (3.3)	7.9	CANTAB Spatial Memory Span	Spatial span	NBRS: r = -.52
					CANTAB Spatial Working Memory	Spatial working memory	NBRS: r > .33
					CANTAB Tower of London	Planning	NBRS: r > .33

Negative coefficients indicate that the concern factors has a negative impact on executive function in very preterm children.

CANTAB = Cambridge Neuropsychological Testing Automated Battery; D-KEFS = Delis-Kaplan Executive Function Scale; GA = Gestational Age; NBRS = Neurobiological Risk Score; NEPSY = A Developmental NEuroPSYchological Assessment; SES = Social Economic Status.

[a]Neurobiological risk included the incidence of specific medical problems including RDS, and patent ductus arteriosus. Severity of illness was estimated in terms of days on oxygen, days on intermittent positive-pressure ventilation, and whether the child was discharged home on oxygen.

Rotterdam, The Netherlands. For an elaborate description of the inclusion procedure of very preterm children we refer to earlier publications.[16-17] The term group was recruited from three regular primary schools located in the same neighborhoods as schools attended by the very preterm children and included children without histories of prematurity (gestational age > 37 weeks), perinatal complications, and neurological disorders.

Minor neurosensory dysfunctions as observed in participating children are presented in TABLE 2 and included (1) vision corrected to normal with contact lenses or glasses, (2) hearing loss corrected to normal with hearing aids, (3) spastic unilateral cerebral palsy, classified according to standards of the Surveillance of Cerebral Palsy in Europe (SCPE, 2000).

Neonatal Risk Factors

We determined an a priori set of neonatal risk factors, which have been proven predictive for outcomes in the literature.[1,9] In addition, these factors are registered in

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TABLE 2 Sample Characteristics of the Very Preterm and Term Group

	Groups					
	Very Preterm (*n* = 200)			Term (*n* = 230)		
Age[a], mean (SD), range, y	8.2	2.5	4.0-12.0	8.3	2.3	4.0-12.0
Gestational age, mean (SD), range, wk	28.1	1.4	24.5-30.0	39.9	1.2	37.0-43.0
<28 wk, *n* (%)	87.0	43.5		0.0	0.0	
Birthweight, mean (SD), range, g	1013.0	287.0	460-1900	3578.0	482.0	2500-5025
<1500 g, *n* (%)	191.0	95.5		0.0	0.0	
Boys, *n* (%)	106.0	53.0		106.0	46.1	
Estimated IQ[b]	93.3	15.8	70.0-138.0	105.0	13.4	70.0-141.0
Parental education[c], *n* (%)						
High	45.0	23.1		109.0	47.3	
Intermediate	75.0	38.2		79.0	34.3	
Low	80.0	38.7		33.0	14.3	
Minor neurosensory dysfunction, *n* (%)	37.0	18.5		13.0	5.6	
Minor vision loss or corrected with contact lenses or glasses	26.0	13.0		13.0	5.6	
Minor hearing loss or corrected with hearing aids	5.0	2.5		0.0	0.0	
Spastic unilateral cerebral palsy	6.0	3.0		0.0	0.0	

[a]Age of the very preterm children is not corrected for prematurity.

[b]IQ was estimated using the subtests Vocabulary and Block Design of the WISC-III,[19] or Wechsler Primary and Preschool Scale Intelligence-Revised (WPPSI-R)[52](depending on the child's age). Subtest scores were converted into a composite score that was used to calculate an estimated IQ, which correlates highly (0.9 range) with full-scale IQ.[53]

[c]Highest of two parents. Low = primary education only or prevocational secondary education; intermediate = 3-year secondary education or middle vocational education; high = higher professional, university training or PhD.

all circumstances despite the retrospective nature of the data collection and include gestational age, birth weight standard deviation score (SDS), postnatal growth at six weeks corrected age, IVH grade III and IV, oxygen dependency at 36 weeks postconceptional age, and the incidence of meningitis and necrotizing enterocolitis stage II or III. Postnatal steroids were left out as were Apgar scores since these factors may not have been reliably registered.

Social Environmental Circumstances

Parental education served was classified according to the classification system of Statistics Netherlands (2004),[18] which distinguishes three levels of education: low, intermediate, and high. 'Low' refers primary education only or prevocational secondary education; 'intermediate' refers to 3-year secondary education or middle vocational education, and 'high' refers to higher professional and university training, or PhD. The educational level rated as most prestigious out of mother and father was chosen to define parental education.

Executive Function Tests

For the purposes of the present study we used executive function tests on which our very preterm sample has been found to perform significantly poorer than term children.[16] These tests included the 1) backwards condition of the Digit Span subtest of the Wechsler Intelligence Scale for Children-III[19] which measures *verbal working memory*, 2) the Spatial Span subtest of the Cambridge Neuropsychological Testing Automated Battery (CANTAB)[20-21] which measures *spatial working memory*, 3) the Verbal Fluency test[10] which measures the ability to generate as many different verbal solutions for a particular instruction as possible, 4) the CANTAB subtest Stockings of Cambridge[20-21] which measures *spatial planning*, and 5) the Stop Signal test[22] which measures *inhibitory control*. For an elaborate description of the tests and outcome variables derived we refer to an earlier publication. [16]

Outcome variables derived from the executive function tests were subjected to factor analysis to remove redundancies and increase reliability for the purposes of subsequent analyses.[23] Three factors were extracted ($\chi^2(36) = 44.31$, $p = 0.16$), of which the first factor consisted of outcome measures derived from the Digit Span and Verbal Fluency tests, with factor loadings in the total sample ranging between 0.78 and 0.83 ($p_s < 0.001$), and was labeled 'verbal working memory/fluency factor'. The second factor consisted of outcome measures derived from the Spatial Span and Stockings of Cambridge, with factor loadings in the total sample ranging between 0.28 and 0.91 (*ps* < 0.001), and was labeled 'spatial working memory/planning factor'. The third factor consisted of the outcome measures derived from the Stop Signal test, with factor loadings for the total sample ranging between 0.70 and 0.97 (p_s < 0.001), and was labeled 'inhibitory control factor'. Total percent of variance explained ranged from 69% for the first factor to 94% for factor three.

Procedure of Data Collection

This study was part of a larger study into the neurobehavioral outcomes of very preterm children which was carried out in the years 2007 and 2008. Very preterm children were assessed at the Sophia Children's Hospital Rotterdam, while term children were assessed at their schools. Assessments were performed by specifically trained experimenters using standardized instructions. Written informed consent was obtained from all parents of participating children. The medical ethics review board of the Erasmus University Medical Centre Rotterdam approved the study protocol.

Statistical Analyses

For outcome variables derived from the Verbal Fluency, Digit Span, and Stop Signal test, there were missing data (<7.0%) which resulted from either examiner error or child noncompliance. These missing values were imputed by means of maximum likelihood estimation (Expectation Maximization).[15,24] Missing data for outcome variables of the Spatial Span and Stockings of Cambridge test (17.3% and 6.5%, respectively) resulted from hardware problems and were not imputed.

Univariate analyses of variance were used to study group differences between very preterm and term children for sample characteristics and executive function factor scores. Effect sizes were expressed in terms of standardized mean differences (SMD) with effect sizes of 0.20, 0.50, and 0.80 referring to small, medium, and large effects, respectively.[25]

Multiple linear regression analyses subsequently examined effects of neonatal risk factors and parental education on executive function factor scores of the very preterm sample. First, analyses were performed with neonatal risk factors. Second, analyses were performed with parental education. Third, analyses were performed on neonatal risk factors and parental education variables together. This approach enabled to determine the unique contribution of each set of these variables to executive function. All regression analyses were adjusted for sex and age of the child. If main effects of sex or age were significant, then interaction effects with the neonatal risk factors and parental education were tested. If there were significant interaction effects with age, then analyses were repeated on two subsamples, one with children of 4.0 to 7.9 years (n = 88), and one with children of 8.0 to 12.0 years (n = 109). As there were small to moderate correlations among neonatal risk factors, there was no evidence for critical multicollinearity (all VIF values < 1.28). Results were expressed in unstandardized regression coefficients with their accompanying confidence intervals (CI) and standardized regression coefficients (β) with values of 0.10, 0.30, and 0.50, referring to small, medium, and large effects, respectively.[25] All analyses were performed in SPSS 17.0 and p-values of < 0.05 (two-tailed) were considered statistically significant.

RESULTS

Sample Characteristics

TABLE 2 presents sample characteristics for the very preterm and term group. As expected, very preterm children had a significant lower gestational age (p < 0.001), lower mean birthweight (p < 0.001), lower mean IQ (p < 0.001, SMD = 0.80), lower level of parental education (p < 0.001), and more minor neurosensory dysfunctions (p < 0.001) than term children. There were no group differences for sex (p = 0.29), and age at assessment (p = 0.81). Forty-two children were 4 to 6 years of age, 46 children were 6 to 8 years of age, 54 children were 8 to 10 years of age, and 55 children were 10 to 12 years of age. TABLE 3 presents the neonatal risk factors and parental education of very preterm children entered in the regression analyses.

TABLE 3 Neonatal Risk Factors and Parental Education of Very Preterm Children Entered in Regression Analyses

Neonatal risk factors			
Gestational age, mean (*SD*) (range), weeks	28.1	(1.4)	24.5-30.0
Birthweight SDS, mean (*SD*) (range), g	-0.3	(1.1)	-.39-2.6
Weight at 6 weeks CA, mean (*SD*) (range), g	4287.4	(967.6)	2120.0-7530.0
Meningitis or NEC stage II or III[a], *n* (%)	12.0	(6.0)	
Intraventricular hemorrhage > grade II, III, or IV	30.0	(15.1)	
Oxygen dependence at 36 weeks PCA[b], *n* (%)	22.0	(11.0)	
Parental education			
Parental education low, *n* (%)	80.0	(23.1)	
Parental education intermediate, *n* (%)	75.0	(38.2)	
Parental education high, *n* (%)	45.0	(38.7)	

N = 200. CA = corrected age; NEC = Necrotizing Enterocolitis; PCA = postconceptional age; SDS = standard deviation score; SD = standard deviation.

[a]NEC was defined according to criteria given by Bell et al.[54]

[b]Oxygen Dependence at 36 weeks PCA is an indication of chronic pulmonary problems.[55]

TABLE 4 Associations Between Executive Function, Neonatal Risk Factors, and Parental Education

		Verbal working memory/fluency					Spatial working memory/planning					Inhibitory control				
Age groups	Factors	*B*	*CI*		*β*	*p*	*B*	*CI*		*β*	*p*	*B*	*CI*		*β*	*p*
	Gestational age	-.02	-.10	.06	-.03	.61	-.04	-.14	.06	-.07	.46	.03	-.05	.12	.07	.40
4.0 to 7.9 years	Birthweight SDS	**.10**	**.00**	**.19**	**.16**	**.04**	.02	-.11	.15	.04	.72	.01	-.14	.16	.02	.87
8.0 to 12.0 years	Birthweight SDS	-.01	-.13	.12	-.01	.91	-.11	-.23	.01	-.20	.07	.02	-.03	.08	.10	.37
	Weight at 6 weeks CA	-.01	-.10	.08	-.02	.78	-.04	-.16	.07	-.08	.46	.00	-.09	.10	.01	.91
	Oxygen dependence at 36 weeks PCA	.04	-.28	.35	.01	.81	-.01	-.39	.37	.00	.96	.03	-.28	.35	.02	.83
	Intraventricular hemorrhage > grade II	-.22	-.47	.03	-.09	.09	.05	-.26	.36	.03	.73	.08	-.17	.34	.05	.52
	Meningitis or NEC stage II or III	.32	-.07	.71	.08	.10	-.39	-.92	.13	-.12	.14	.18	-.21	.57	.07	.37
4.0 to 7.9 years	Parental education intermediate	**.30**	**.05**	**.55**	**.19**	**.02**	**.38**	**.05**	**.72**	**.29**	**.03**	-.16	-.55	.23	-.09	.42
8.0 to 12.0 years	Parental education intermediate	.15	-.12	.42	.11	.27	.22	-.05	.49	.18	.11	-.08	-.19	.04	-.14	.20
4.0 to 7.9 years	Parental education high	**.25**	**.03**	**.47**	**.19**	**.02**	.16	-.14	.46	.14	.30	.18	-.17	.53	.12	.30
8.0 to 12.0 years	Parental education high	.24	-.05	.52	.17	.10	.12	-.15	.39	.10	.38	**-.15**	**-.27**	**-.03**	**-.27**	**.01**

N = 200. CA = corrected age; NEC = necrotizing enterocolitis; PCA = postconceptional age; SDS = standard deviation score

Significant ($p < 0.05$) associations are shown in bold type.

6

Executive Function Test Performance

Very preterm children had significantly lower verbal working memory/fluency factor scores (0.49 SMD), lower spatial working memory/planning factor scores (0.44 SMD), and higher inhibitory control factor scores (0.52 SMD) than term children ($p_s < 0.001$).

Associations Between Neonatal Risk Factors, Parental Education and Executive Function

TABLE 4 displays the unstandardized regression coefficients and their accompanying CI's, as well as the standardized regression coefficients for the associations between both neonatal risk factors and parental education, and executive function.

Only in the 4.0 to 7.9 years children birthweight SDS was significantly associated with the verbal working memory/fluency factor ($\beta = 0.16$) indicating that dysmaturity was positively related to verbal working memory/fluency performance in the youngest very preterm children. There was tendency ($p < 0.09$) for IVH grade II and higher to be negatively associated with the verbal working memory/fluency factor. Other neonatal risk factors were not associated with executive function. Intermediate and high levels of parental education were significantly associated with better verbal working memory/fluency, spatial working memory/planning performance, and inhibitory control, but these effects interacted with age ($\beta_s > 0.15$, $p_s < 0.01$) (please see TABLE 4). The coefficients in TABLE 4 show that these effects of parental education on verbal working memory/fluency and spatial working memory/planning were found in the younger very preterm children aged 4.0 to 7.9 years and not in very preterm children aged 8.0 to 12.0 years. Effects of parental education on inhibitory control were observed in the very preterm children aged 8.0 to 12.0 years.

DISCUSSION

Very preterm children are at high risk for impaired executive functioning.[13,15-16] Objective of this study was to examine the predictive value of neonatal risk factors and parental education for impaired executive functioning in very preterm children and to examine whether these influences vary with sex and age.

Except for early prenatal growth in terms of degree of dysmaturity which was related to verbal working and fluency skills in 4.0 to 7.9 year olds, neonatal risk factors were not predictive for poor executive function in very preterm children. There was a trend that IVH grade II or higher was associated with poorer working memory and fluency skills, although this finding should be interpreted with caution since only few children in the sample had severe IVH. The lack of associations between these neonatal risk factors and executive function converges with other large sample studies on this issue,[26-27] but also contradicts a number of earlier studies.[9,28-29] We did not find evidence that unfavorable postnatal growth was related to poor executive function, although there is some evidence that it is important for neurocognitive function in this population.[30-31] Neonatal complications as examined in the present study may be more likely associated with moderate to severe disabilities than with 'subtle' neurocognitive deficits.[32] Lack of significant associations may be due to the focus on 'apparently normal', non-disabled very preterm children. Another reason may be that relations between risk factors and outcomes appear to be domain specific.[33] Neonatal risk factors, such as growth or brain injury, tend to better predict perceptual-motor abilities,[34] whereas social risks are better predictors of verbal abilities, IQ, and behavioral functioning.[35]

Parental education was positively associated with executive function. This finding not only agrees with earlier studies on this issue,[15,26,29] but also with earlier findings that parental factors have greater impact on very preterm children's neurocognitive functioning than neonatal risk factors.[36] In our study, children with highly educated parents had better working memory, verbal fluency, and planning skills, than children with low educated parents. Relationships between parent and child executive abilities are for a great part explained by shared genes.[37] Besides the genetic benefits these children have, they as well take advantage of their highly educated parents providing them a more optimal environment in which early problem solving skills are stimulated.[38] The language use in parent-child interaction in high education families is also different compared to that of low education families.[38] Highly educated parents, in particular mothers, talk more, use a richer vocabulary, and read more to their children than those mothers limited to a low school education.[39] Interesting were the interaction effects with age. Beneficial effects of parental education on working memory, fluency, and planning skills, in particular occurred in the youngest very preterm children. This agrees with studies with term children suggesting that the influence of parental education is stronger in young than in older children,[38,40] It is likely that this relationship can for a great part be accounted for by the rapid language acquisition which is characteristic for children at early school ages.[41] In contrast, beneficial effects of parental educational level on inhibitory control occurred in the eldest subgroup of very preterm children. We have previously shown that inhibitory control improves over time in this sample of very preterm children.[16] The present results suggest that this improvement, however, only occurs in children with highly educated parents. Such age-related improvements which depend on quality of social economic circumstances in preterm children have been described before for more 'general' cognitive functions, [35] however, future research may further clarify this issue.

Limitation of the study is the restricted assessment of neonatal risk and social environmental risk factors. Although we included factors that have been identified as influential on outcomes in very preterm children this array of factors was limited. We may therefore have underestimated the contribution of biomedical risk, since other perinatal morbidity, not subject of this study, may as well have a significant impact on executive function in very preterm children. In addition, we did not include more proximal indices of social environmental circumstances such as neighborhood, presence of resources, opportunities to engage in sports or hobbies, which may, as children grow older, positively contribute to executive functioning.[42]

Conclusion

In agreement with the literature, our study did not find convincing evidence that an adverse neonatal history is an important predictor for impaired executive function in very preterm children. Neither delayed postnatal growth, chronic lung disease, nor severe inflammatory diseases such as NEC or meningitis, were correlated with executive function in later life. Although very preterm children's brain development may be impaired by such destructive conditions,[43] in this subsample of very preterm children without overt neurosensory disabilities, not specific neonatal risk factors account for impaired executive function following very preterm birth but rather the underlying diffuse white matter pathology and frontal lobe regions abnormalities as proposed by recent studies. [44-47] These brain abnormalities may result from interrupted maturation of cortical and subcortical connections due to preterm delivery[43] and subsequent stressful events.[48] Preterm delivery has, yet independent of subsequent morbidity, effects on white matter quality shown by studies which found that even very preterm children with normal-appearing white matter on conventional MRI may have diffuse excessive high signal intensity significantly related to neurodevelopmental delays.[49] Therefore, we propose that instead of using neonatal risk factors as predictors, anatomical brain changes could be used in the identification of children surviving preterm birth who may be at risk for neurocognitive impairments.[50]

Stimulating home environments may, however, moderate these effect of very preterm birth on executive function as we found a positive association between parental education and executive function. Neural plasticity evoked by optimal environmental circumstances may compensate for injured white and grey matter perhaps by increasing the density of synapses and other neurocellular processes, thereby maximizing efficiency of neural wiring.[51] Given the high incidence of academic and behavior problems[13] related to poor executive function in very preterm children,[3-9] major efforts should be made to create such optimal (home) environments for very preterm children. A shift from improvements focusing at the neonatal ward only, towards a more balanced approach trying to optimize both the perinatal treatment and creating an adequate home environment is warranted to reduce the personal and societal burden associated with preterm birth.

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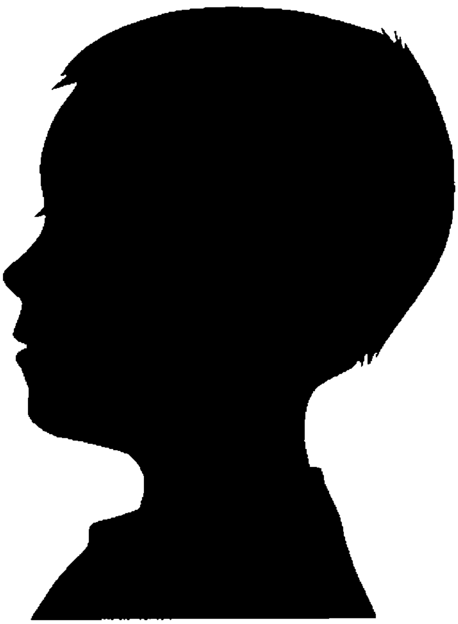
Chapter 7

Executive function and IQ predict mathematical deficits and attention problems in very preterm children

Submitted



ABSTRACT

Objective

To examine the impact of executive functioning on mathematical and attention problems in very preterm (gestational age ≤ 30 weeks) and term children.

Methods

Two-hundred very preterm (mean age 8.2 ± 2.5 years) and 230 term children (mean age 8.3 ± 2.3 years) without severe disabilities, born between 1996 and 2004, were assessed with measures of mathematics, executive functioning, processing speed, and IQ, in preschool and in primary school. Parents and teachers reported on attentional functioning using standardized behavior questionnaires. Executive functioning was, over and above processing speed and IQ, regressed on mathematical skills and attentional functioning. Interactions with group (very preterm or term) were examined.

Results

Very preterm children had significantly lower executive functioning scores (> 0.44 SMD), poorer math achievement (> 0.60 SMD), and higher ratings of attention problems (> 0.46 SMD) than term peers in preschool and primary school. Processing speed indices were not significantly predictive for mathematical and attention problems ($p_s > 0.16$). IQ significantly predicted mathematical performance ($\beta_s > 0.16$, $p_s < 0.04$). Executive functioning was, over and above IQ, significantly predictive for mathematical problems ($\beta_s < 0.07$, $p_s < 0.03$) and attention problems ($\beta_s < 0.18$, $p_s < 0.03$) only in primary school. Associations between IQ, executive functioning, and teacher ratings of attention problems, were stronger for very preterm than for term children (interaction effect: $\beta_s > -0.16$, $ps < 0.04$).

Conclusions

Very preterm birth is associated with medium-sized deficits in mathematics and attention problems. Impaired IQ and executive function scores are important predictors for these adverse outcomes.

INTRODUCTION

Most very preterm (gestational age ≤ 30 weeks) infants survive without major disabilities.[1] However, a majority of these 'non-disabled' survivors suffer from academic and behavior problems that persist into adulthood.[2] About 70% of this population has special educational needs, and the social and economic burden is large. The most pronounced academic and behavior problems are mathematical deficits and attention problems.[3-4] We have recently shown that preschool mathematical abilities comprising numerical reasoning skills are already substantially impaired in very preterm children.[5] To enable early intervention, more insight in mechanisms involved in the onset of these mathematical and attentional problems is needed.

A large body of literature on term children has demonstrated that higher-order neurocognitive processes, the so-called executive functions (EF) are the crucial explanatory mechanism underlying mathematical deficits and behavior problems.[6-13] EF are prefrontal brain functions that control thought and behavior. Typical lists of EF include the capacity to mentally manipulate information in mind (i.e. working memory), generating as many different solutions for a particular problem as possible (i.e. verbal fluency), developing strategies to reach a future goal (i.e. planning), and inhibiting responses to irrelevant stimuli (i.e. inhibitory control).[10,14-15]

Research has consistently described impaired EF in very preterm children.[3,16-18] Nevertheless, studies linking EF to academic achievement and behavioral difficulties in very preterm children remain scarce.[19-23] Available studies have shown that very preterm children's poor inhibitory control and working memory skills are related to academic underperformance and inattentive behavior. Slowed speed of processing, however, has been suggested to underlie this relationship.[20,22] Slowed processing speed results from white matter abnormalities,[24] a phenomenon frequently observed in very preterm children.[25-27] Compromised white matter may as well result in great fluctuations in speed.[28] Such fluctuations induce major trial-to-trial variations in performance which, for instance, has recently been postulated as the specific deficiency in AD(H)D.[29-31] Whether such fluctuations in speed underlie attention deficits in very preterm children has not been examined yet.

Aim of this study was to capture the specific contribution of EF to mathematical skills and attention of very preterm and term children in preschool and primary school. Effects of poor EF on these adverse outcomes were calculated over and above effects of processing speed and IQ. Analyses were performed with an extensive array of EF measures on a large sample of very preterm and term children, aged 4.0 to 12.0 years, who were comparable in age and sex, and free of major disabilities.

METHODS

Participants

The sample of 200 very preterm (gestational age ≤ 30 weeks) children was derived from all (*n* = 706) very preterm surviving singletons admitted between 1996-2004 to the neonatal intensive care unit of the Erasmus University Medical Centre, Sophia Children's Hospital Rotterdam, The Netherlands. Details on the inclusion procedure and neonatal characteristics of the very preterm sample have been previously described.[24] The term group (*n* = 230) was recruited from three regular schools located in the same neighbourhoods as schools attended by the very preterm children, and included children without histories of prematurity (gestational age > 37 weeks), perinatal complications, and neurological disorders. The present study was carried out in the years 2007 and 2008.

Minor neurosensory dysfunctions as observed in participating children are presented in TABLE 1 and included (1) vision corrected to normal with contact lenses or glasses, (2) hearing loss corrected to normal with hearing aids, (3) spastic unilateral cerebral palsy classified according to standards of the Surveillance of Cerebral Palsy in Europe (SCPE, 2000).

Outcome Measures

Mathematics were assessed using standardized tests which are part of the Dutch National Pupil Monitoring System.[32] Mathematical skills in preschool were assessed with the Numerical Reasoning test[33] which measures classifying, sorting, comparing, and counting of objects. Mathematics in primary school was assessed with the Mathematics test[34] measuring the ability to solve written computational problems of addition, subtraction, multiplication, division, the notion of time, and use of money.

A*ttention ratings* were provided by parents and teachers using the Attention Problems scale of the Child Behavior Checklist (CBCL/1-5 or CBCL/6-18; depending on the child's age),[35-36] and its teacher equivalent: the Teachers Report Form (TRF/1-5 or TRF/6-18),[35-36] and the primary school Inattention subscales of the Disruptive Behavior Disorders parent and teacher rating scales (DBD/6-12).[37-38] To enhance reliability we calculated an averaged score among the parent DBD and CBCL attention scales, and among teacher DBD and TRF attention scales, as the intercorrelations were high (r_s>

TABLE 1 Sample Characteristics of the Very Preterm and Term Group

	Groups					
	Very Preterm (n = 200)			Term (n = 230)		
Age[a], mean (SD), range, y	8.2	2.5	4.0-12.0	8.3	2.3	4.0-12.0
Gestational age, mean (SD), range, wk	28.1	1.4	24.5-30.0	39.9	1.2	37.0-43.0
<28 wk, *n* (%)	87.0	43.5		0.0	0.0	
Birthweight, mean (SD), range, g	1013.0	287.0	460-1900	3578.0	482.0	2500-5025
<1500 g, *n* (%)	191.0	95.5		0.0	0.0	
Boys, *n* (%)	106.0	53.0		106.0	46.1	
Estimated IQ[b]	93.3	15.8	70.0-138.0	105.0	13.4	70.0-141.0
Parental education [c], *n* (%)						
High	45.0	23.1		109.0	47.3	
Intermediate	75.0	38.2		79.0	34.3	
Low	80.0	38.7		33.0	14.3	
Minor neurosensory dysfunction, *n* (%)	37.0	18.5		13.0	5.6	
Minor vision loss or corrected with contact lenses or glasses	26.0	13.0		13.0	5.6	
Minor hearing loss or corrected with hearing aids	5.0	2.5		0.0	0.0	
Spastic unilateral cerebral palsy	6.0	3.0		0.0	0.0	

[a]Age of the very preterm children is not corrected for prematurity.

[b]IQ was estimated using the subtests Vocabulary and Block Design of the WISC-III,[19] or Wechsler Primary and Preschool Scale Intelligence-Revised (WPPSI-R)[52](depending on the child's age). Subtest scores were converted into a composite score that was used to calculate an estimated IQ, which correlates highly (0.9 range) with full-scale IQ.[53]

[c]Highest of two parents. Low = primary education only or prevocational secondary education; intermediate = 3-year secondary education or middle vocational education; high = higher professional, university training or PhD.

0.75, $p_s < 0.001$). This average score was calculated for parent and teacher ratings separately, since inter-rater correlations were moderate ($r < 0.52$).[39].

P*rocessing speed* was measured with mean reaction time (MRT) calculated across correctly executed go-trials of the Stop Signal test.[40-41] An index for *fluctuations in processing speed* was derived from the standard deviation of the reaction times on correctly executed go-trials of the Stop Signal test divided by MRT (SD of RT/MRT).[41-42]

I*Q* was estimated using the subtests Vocabulary and Block Design of the Wechsler Intelligence Scale for Children (WISC-III-NL)[43], or Wechsler Primary and Preschool Scale Intelligence-Revised (WPPSI-R)[44] (depending on the child's age). Subtest scores were converted into a composite score that was used to calculate an estimated IQ, which correlates highly (.9 range) with full-scale IQ.[45]

Executive functioning was assessed by a test battery consisting of 1) verbal working memory, assessed using the backwards condition of the Digit Span subtest of the WISC-III-NL.[43] Series of digits that were read by the examiner (one digit per second) were to be repeated in the reverse order. The dependent measure was the total number of correctly repeated series. 2) Spatial working memory, assessed using the Spatial Span subtest of the Cambridge Neuropsychological Testing Automated Battery (CANTAB).[46-47] Children viewed a lighted sequence of squares and were required to reproduce the sequence by touching items on a touchscreen in the same order as originally illuminated. The dependent measure was the maximum span reached successfully. 3) Verbal fluency, measured in a test[10] that required children to name as many examples of two specific categories: "animals" and "things you can eat or drink" within a 40-second time frame. The dependent measure was the total number of correct responses. 4) Planning, assessed using the CANTAB subtest Stockings of Cambridge,[46-47] which required children to solve problems by moving colored circles between three locations in a prescribed number of moves. Dependent measures derived were number of problems solved, planning time, and execution time. 5) Inhibitory control, measured with the Stop signal test[40] that required a child to respond as quickly and accurately as possible to a go-stimulus and to inhibit the response if a stop-stimulus was presented. Dependent measures derived included errors of commission and omission, and stop signal reaction time, an estimate of the time a child needed to stop his or her response (defined as MRT minus the mean delay).[19]

EF dependent variables were subjected to factor analysis to remove redundancies and increase reliability for the purposes of subsequent analyses.[48] Three factors were extracted ($\chi^2(36) = 44.31$, $p = 0.16$), of which the first factor consisted of dependent measures derived from the Digit Span and Verbal Fluency tests, with factor loadings in the total sample ranging between 0.78 and 0.83 ($p_s < 0.001$).This factor was labelled 'verbal working memory/fluency factor'. The second factor consisted of dependent measures derived from the CANTAB Spatial Span and CANTAB Stockings of Cambridge, with factor loadings in the total sample ranging between 0.28 and 0.91 ($p_s < 0.001$). This factor was labelled 'Spatial Working Memory/Planning factor'. The third factor consisted of the dependent measures derived from the Stop Signal test, with factor loadings for the total sample ranging between 0.70 and 0.97 ($p_s < 0.001$). This factor was labelled 'inhibitory control factor'.

Procedure of Data Collection

Data on mathematics were obtained from the children's schools. For very preterm children, completion of behavior questionnaires and assessment of EF and IQ took place at the Erasmus University Medical Centre Rotterdam Sophia Children's Hospital Rotterdam.

Term children were assessed at their schools. Parents of all participating children provided informed consent. The medical ethics review board of the Erasmus University Medical Centre Rotterdam approved the study protocol.

Statistical Analyses

Data on mathematics were available for 75.3% of the participating children. For the remaining children data on mathematics were not available because they were either in special education (n = 24), or their school used a different pupil monitoring system (n = 24), or they were too young (n = 58) to be assessed with the mathematics test at the time of participation in our study.[5] In preschool, parent ratings of attention were available for all children, but teacher ratings of attention were available for 70.0% of the children. In primary school, parent ratings of attention were available for 80.7% of the children and teacher ratings of attention were available for 74.1% of the children.

For dependent variables derived from the Verbal Fluency, Digit Span, and Stop Signal test, there was missing data (< 7.0%) which resulted from either examiner error or child noncompliance. These missing values were replaced by means of maximum likelihood estimation (Expectation Maximization).[16,48] Missing data for dependent variables of the Spatial Span and Stockings of Cambridge test (17.3% and 6.5%, respectively) resulted from hardware problems and were not replaced.

Analyses were performed for available data in preschool and primary school, separately (please see TABLE 4 for the number of children included in all separate analyses). Univariate analyses of variance were used to study group differences between very preterm and term children for sample characteristics, EF factor scores, processing speed indices, IQ, and both mathematics and attentional functioning. Effect sizes were expressed in terms of standardized mean differences (SMD) with effect sizes of 0.20, 0.50, and 0.80 referring to small, medium, and large effects, respectively.[49]

Multiple linear regression analyses subsequently examined effects of the independent variables very preterm birth status, processing speed indices, IQ, and EF factor scores, on the dependent variables mathematics and attentional functioning. This approach enabled to determine the unique contribution of each of these variables to mathematical and attention problems. If main effects of processing speed indices, IQ, or the EF factor scores, were significant, then interaction effects with group (very preterm or term) were calculated to examine whether any of these variables had significantly different effects in very preterm and term children. All analyses adjusted for age and parental education. Results were expressed in standardized regression coefficients (β) with values of 0.10, 0.30, and 0.50, referring to small, medium, and large effects, respectively. [49] All analyses were performed in SPSS 17.0 with standardized scores (*z*-scores) and *p*-values of < 0.05 (two-tailed) were considered statistically significant.

RESULTS

Group Differences

TABLE 1 presents sample characteristics for the very preterm and term group. As expected, very preterm children had a significantly lower mean gestational age ($p < 0.001$), lower mean birth weight ($p < 0.001$), lower mean level of parental education ($p < 0.001$), and more minor neurosensory dysfunction ($p < 0.001$) than controls. There were no significant group differences for age at assessment ($p = 0.8$), or sex ($p = 0.3$).

TABLE 2 displays the mean z-scores, accompanying *SE*s, and standardized mean differences (SMD), for IQ, processing speed indices, and EF factor scores. Very preterm children had a significantly lower mean IQ ($p < 0.001$) and slower and more fluctuating processing speed ($p_s < 0.001$) than control children. Very preterm children had significantly lower verbal working memory/fluency factor scores, lower spatial working memory/planning factor scores, and higher inhibitory control factor scores, than control children ($p_s < 0.001$).

TABLE 2 Mean Z-Scores, Accompanying Standard Errors, and Standardized Mean Differences for Estimated IQ, Processing Speed Indices, and EF Factor Scores

	Very Preterm (n = 200)	Term (n = 230)	
	M (SE)	*M (SE)*	*SMD*
Estimated IQ[a]	.04 (.14)	.75 (.11)	.80***
Speed	.01 (.13)	-.34 (.10)	.39***
Speed Fluctuations	.34 (.14)	-.35 (.11)	.70***
Verbal Working Memory/Fluency	.17 (.10)	.45 (.08)	.49***
Spatial Working Memory/Planning	.01 (.14)	.37 (.11)	.44***
Inhibitory Control	.16 (.14)	-.28 (.11)	.52***

Univariate analyses of variance calculated Standardized Mean Differences (SMD) while controlling for age, parental education, and sex.

[a]Very Preterm Group Mean IQ (SD)= 93.3 (15.5); Term Group Mean IQ (SD)= 105.0 (13.6).

***$p < .001$.

TABLE 3 displays the mean z-scores, *SE's*, and standardized mean differences (SMD), for mathematics and attention ratings in preschool and primary school, and correlations with EF factor scores. Mathematical skills in both preschool and primary school were

TABLE 3 Mean Z-Scores, *SE's*, Standardized Mean Differences for Mathematics, and Attention Ratings, and Correlations With EF Factors In Preschool and Primary School

	Groups			Correlations with EF Factor Scores (Total Sample)		
	Very Preterm	Term		Verbal Working Memory/ Fluency	Spatial Working Memory/ Planning	Inhibitory Control
	M (SE)[a]	*M (SE)*[a]	*SMD*	*r*	*r*	*r*
Preschool						
Mathematics (n = 55)[b]	-.37 (.16)	.34 (.20)	.85**	.50**	.36*	-.29**
CBCL/1-5 Attention Scale (n = 117)[b]	.38 (.14)	-.30 (.14)	.68***	-.22*	-.15	.29**
TRF/1-5 Attention Scale (n = 73)[b]	.47 (.18)	-.42 (.19)	.89***	-.26*	-.23	.11
Primary School						
Mathematics (n = 256)[b]	-.17 (.11)	.46 (.11)	.60***	.66***	.57***	-.51***
CBCL/6-18 Attention Scale (n = 248)[b]	.22 (.09)	-.24 (.10)	.46***	-.27**	-.31**	.25**
TRF/6-18 Attention Scale (n = 233)[b]	.32 (.10)	-.32 (.11)	.64***	-.24***	-.34***	.37***
DBD Parent Attention Scale (n = 300)[b]	.24 (.08)	-.24 (.08)	.48***	-.21***	-.28***	.35***
DBD Teacher Attention Scale (n = 300)[b]	.31 (.09)	-.27 (.07)	.58***	-.16**	-.19**	.14*

CBCL = Child Behavior Checklist, DBD = Disruptive Behavior Disorders Rating scale. EF = Executive Function. SE = Standard Error. SMD = Standardized Mean Difference. TRF = Teachers Report Form.

[a]Means and *SE*s are adjusted for age, parental education, and sex.

[b]Cell sizes differ due to availability of data.

*p < .05, **p < .01, ***p < .001.

significantly poorer in very preterm children than in controls (p_s < 0.003). Very preterm children had significantly higher parent and teacher ratings of attention problems in preschool as well as in primary school (p_s < 0.001).

Predictors of Mathematics and Attentional Functioning

TABLE 4 displays the standardized regression coefficients for the relationships between processing speed, IQ, EF factor scores, and both mathematics and attention problems in preschool and primary school separately.

In preschool, very preterm birth status and processing speed indices were not significantly associated with mathematical skills (p_s > 0.48). A higher IQ score was significantly associated with better mathematical skills (β = 0.31, p = 0.04). The interaction effect between group (very preterm or term) and IQ was not significant (β = 0.23, p = 0.22). EF factor scores were not significantly associated with mathematical skills (p_s > 0.32). With regards to attention ratings, very preterm birth status was significantly

TABLE 4 Standardized Regression Coefficients for the Relationship Between Executive Function, Mathematics, and Attention Ratings, in Preschool and Primary School

	Preschool									Primary School								
	Mathematics			Parent Rated Attention			Teacher Rated Attention			Mathematics			Parent Rated Attention			Teacher Rated Attention		
	n	*β*	*p*	*n*	*β*	*p*	*n*	*β*	*p*	*n*	*β*	*p*	*n*	*β*	*p*	*n*	*β*	*p*
Very Preterm Birth Status	55	-.11	.48	117	**.24**	**.03**	73	**.34**	**.04**	256	-.03	.36	248	**.15**	**.04**	233	**.14**	**.05**
Speed	55	.01	.95	117	-.07	.55	73	.07	.68	256	-.01	.70	248	-.08	.27	233	-.05	.51
Speed Fluctuations	55	-.10	.64	117	.03	.87	73	-.28	.16	256	-.02	.62	248	.03	.69	233	.05	.47
IQ	55	**.31**	**.04**	117	-.11	.28	73	-.18	.23	256	**.16**	**.002**	248	-.11	.13	233	**-.23**	**.001**
Verbal Working Memory/Fluency	55	.10	.59	117	.02	.78	73	.06	.69	256	**.10**	**.01**	248	-.04	.58	233	.04	.57
Spatial Working Memory/Planning	46	.14	.32	99	-.01	.96	62	-.04	.91	234	**.07**	**.03**	224	**-.18**	**.03**	208	**-.18**	**.01**
Inhibitory Control	55	-.10	.57	117	.21	.12	73	.17	.34	256	**-.07**	**.03**	248	.06	.48	233	**.24**	**.003**

Multiple linear regression analyses examined effects of successively very preterm birth status, processing speed indices, IQ, and the EF factor scores, on mathematics and attentional functioning.

Trend and significant associations are shown in bold type.

associated with higher parent (β = 0.24, p = 0.03) and teacher (β = 0.34, p = 0.04) ratings of attention problems, respectively. Processing speed indices, IQ, and EF factor scores, were not significantly associated with parent and teacher ratings of attention problems in preschool (p_s > 0.12).

In primary school, very preterm birth status (p = 0.36) and processing speed indices (p_s > 0.62) were not significantly associated with mathematics. Higher IQ scores as well as higher EF factor scores were significantly associated with better mathematical performance (β_s > 0.07, p_s< 0.03). The interaction effect between group (very preterm or term) and IQ was not significant (IQ: β = 0.07, p = 0.07), nor were interaction effects between group and the EF factor scores (β_s < -0.002, p_s > 0.07). With regards to attention ratings, very preterm birth status was significantly associated with higher parent (β = 0.15, p = 0.04) and teacher (β = 0.14, p = 0.05) ratings of attention problems in primary school. Processing speed indices were not significantly associated with parent and teacher ratings of attention problems (p_s > 0.27). Better spatial working memory/planning skills were associated with lower parent ratings of attention problems (β = -0.18, p = 0.03). This effect did not interact with group (β = 0.003, p = 0.97). Higher IQ scores (β = -0.23, p_s > 0.001), better spatial working memory/planning skills (β = -0.18, p = 0.02) and inhibitory control skills (β = 0.24, p = 0.003) were associated with lower teacher ratings of attention problems. Effects of IQ and effects of spatial working memory/planning skills on these teacher ratings of attention problems interacted significantly with group (β_s > -0.16, p_s < 0.04), indicating that these effects were stronger for very preterm than for term children (FIGURE 1). Effects of inhibitory skills did not interact significantly with group (β = 0.11, p = 0.31).

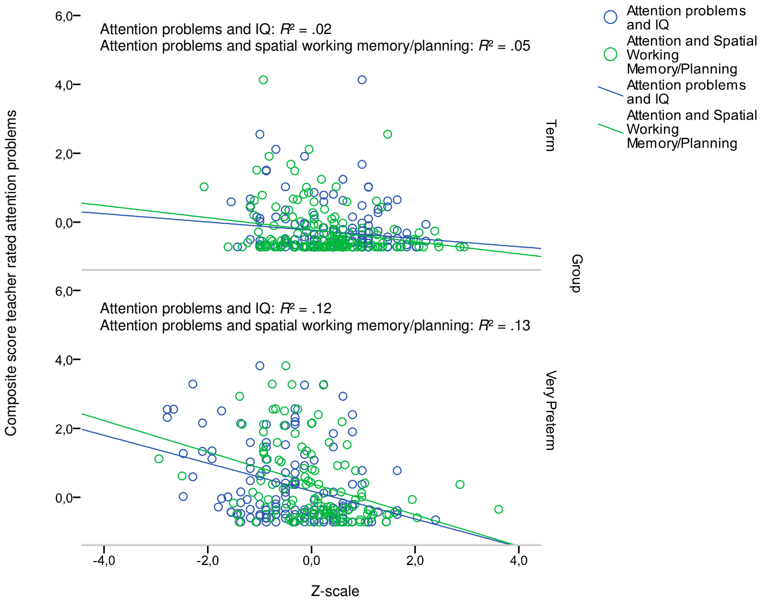


FIGURE 1 Associations Between IQ and Spatial Working Memory/Planning and Teacher Rated Attention Problems for the Term and Very Preterm Children

DISCUSSION

This study demonstrates the robust effects of very preterm birth on achievement in mathematics and attentional functioning but also shows that the excess morbidity in these areas is linked to impaired IQ and EF scores.

Both in preschool and in primary school mathematical skills were explained by group differences in IQ, but not by very preterm birth status. The strong impact of IQ is explained by the fact that our IQ estimate comprises for at least 50% visual-spatial skills (i.e. subtest Block Design) which have been identified as strong predictors for mathematical abilities.[7,50-52] Mathematical skills in primary school were also impacted by EF which converges with the literature on very preterm as well on term children.[9,50-51,53]

Attention problems in preschool were solely predicted by very preterm birth status. The absence of effects of IQ or EF may be caused by the fact that inattentiveness in young children reflects immaturity in behavioral adjustment, rather than a 'true' attention deficit in isolation,[54] which is associated with impaired neurocognitive functioning.[11] In the normal population, attention problems at preschool age appear to be persistent in only 5% of children,[55] and physicians are reluctant in diagnosing attention deficit disorders in young children.[56]

Attention problems in primary school, however, were predicted by IQ and EF. Significant interaction effects with group indicated that these effects of poor cognitive and executive functioning, respectively, were much more important for very preterm than for term children, which suggests a distinct neurocognitive basis for attention problems in very preterm children compared to their term peers.[57] The concerning executive functioning domains included spatial working memory/planning skills which were important for both parent and teacher ratings of inattention, and inhibitory skills which were important for the degree of teacher rated attention problems, findings that converge with the literature.[58-60] The inconsistency between parent and teacher ratings in whether these are associated with EF task performance has been observed previously and has been explained by the fact that teachers may be more optimal informants for attention problems.[61-62] Results confirm strong associations between poor EF and inattention both subserved by fronto-striatal and frontal-parietal networks,[63] and converge with findings of abnormalities in these neural structures.[64-65]

Contrasting earlier studies,[20,22] we did not find effects of processing speed although processing speed was significantly slower and more variable in our very preterm than in term children. Effects of speed observed by earlier studies may be confounded, however, since speed measures were used of which psychometric properties have been questioned and which heavily rely on fine motor coordination,[66-67] which is frequently observed to be impaired in very preterm children.[32-35] The impact of EF in our study was smaller than in earlier studies (e.g.[22-23]) into this issue. A possible explanation may be that EF shares variance with IQ (e.g.[68]) and that in our study effects of EF were calculated while controlling for IQ, whereas in earlier studies effects of EF were compared to that of IQ. Limitations were that data on mathematics achievement were not available for the total sample and the lack of longitudinal assessments which would have enabled to perform growth curve analyses to examine the contribution of EF at preschool age to academic achievement and attentional functioning at the end of primary schooling. Strengths of our study were that we used a larger number of children assessed across a wider age range, than earlier studies did, and that we utilized an array of well-validated EF measures.[18]

Conclusion

Very preterm birth is associated with severe deficits in mathematics and symptoms of inattention. Impaired IQ and EF scores were important predictors for these adverse outcomes. EF was found to be important at the time of primary schooling, and not in preschool, which supports the idea that poor EF hampers the ability to function normally ever since the environment becomes increasingly complex and demanding.[16,69]

Observed links between attention problems, and cognitive and executive functioning, were stronger for very preterm children than for their term peers, a finding of great merit since it opens a new and important window for intervention. Intervention techniques proven to have significant effects include cognitive training programs. Klingberg and colleagues have presented behavioral and neurophysiological evidence in children that, for instance, working memory capacity can be enhanced by systematic training and that training effects also generalize to non-trained tasks requiring working memory capacity.[70-73] In addition, EF has been shown to be highly sensitive to effects of methylphenidate.[41]

The practice of neonatal follow-up care may expand their conventional IQ assessments with EF assessments. Although IQ remains an important predictor for mathematics achievement, the exclusive assessment of IQ may not sufficiently assess the underlying nature of adverse outcomes in terms of poor mathematics and attention problems.

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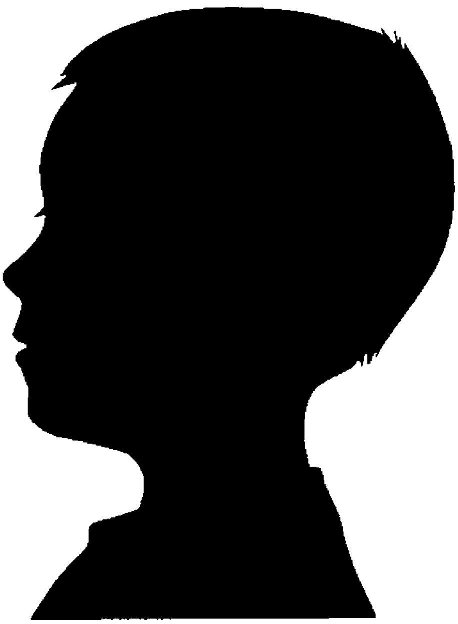
Chapter 8

Summary of the findings and general discussion



SUMMARY OF THE FINDINGS

Aims of this thesis project were to provide a detailed picture of executive function (EF) in very preterm (gestational age ≤ 30 weeks) children of 4.0 to 12.0 years of age and to investigate the predictive role of neonatal and social environmental factors for impaired EF. Having unraveled the currently existing inconsistencies and unclearness on these issues, the project studied the impact of EF on academic achievement and behavior in very preterm children.

Below, findings of the studies undertaken to address these above described aims will be summarized. After this summary, main findings will be discussed in the context of how they refine our understanding of EF in very preterm children and its contribution to the nature of academic and behavioral problems following very preterm birth. Lastly, limitations of which findings are subject to, as well as the clinical implications of the findings and suggestions for future possible studies will be discussed.

The first two studies of this thesis, described in **Chapters 2 and 3**, provide a thorough examination of the severity of academic, behavioral, and EF deficits, in very preterm children.

Chapter 2 quantitatively reviewed published results across different countries on academic and behavior problems, and EF, in very preterm children which enabled to chart the severity of these adverse outcomes in this population. Combined effect sizes showed that very preterm and/or VLBW children scored 0.6 SD lower on mathematics tests, 0.5 SD lower on reading tests, and .8 SD lower on spelling tests, than term born peers. Attention problems were the most pronounced in very preterm and/or VLBW children with teacher and parent ratings being 0.4 SD to 0.6 SD higher than for controls, respectively. Results further demonstrated a decrement of 0.4 SD to 0.6 SD for diverse EF tests. These adverse outcomes were demonstrated to persist into young adulthood.

C**hapter 3** reported on an in-depth study into academic achievement in very preterm children. Two-hundred very preterm children (mean age = 8.2 years, SD = 2.5) born between 1996 and 2004 and without severe disabilities were compared to 230 term children (mean age = 8.3 years, SD = 2.3) of comparable age and sex. The Dutch National Pupil Monitoring System[1] was employed to assess academic achievement in preschool as well as in primary school. In preschool, very preterm children performed comparable to term children in early linguistics, but performed poorer (0.7 SD) in numerical reasoning skills. In primary school, very preterm children performed comparable to term children in reading comprehension and spelling, though performed 0.3 SD lower in complex word reading and 0.6 SD lower in mathematics than term children. Catch-up with peers was shown for reading of simple words, albeit these children continued to lag behind peers in reading of complex words and mathematics. Very preterm children had a higher grade retention rate (25.5%), though grade retention did not improve their academic skills which highlights the need to search for more effective methods to help these children overcome their (pre-) academic weaknesses.

The first research question, i.e. what is the profile of strengths and weaknesses in EF in very preterm children and to what extend does this profile persist from preschool to the end of primary schooling, was addressed in **Chapters 4 and 5**. **Chapter 4** examined a comprehensive range of EF sub-skills including inhibitory control (i.e. prepotent response inhibition and interference control), verbal and spatial working memory, verbal fluency, switching, and planning, in the large cohort of 200 very preterm children as described in Chapter 3. Results demonstrated that impaired EF in these children mainly reflects a permanent lag. Catch-up with term peers was shown only for the subskill inhibitory control, however impairments in verbal and spatial working memory (0.3 SD), verbal fluency (0.5 SD) and planning (0.4 SD), persisted over time. These deficits were independent of IQ and processing speed. These results added to the literature (for an overview please see [2-3]) in that we found that very preterm children catch up with peers in response inhibition, but stay behind in neurocognitive functions as verbal fluency, planning, and working memory. Interestingly, interference control and switching were not impaired in our very preterm sample. Earlier studies employing the Stroop task, a widely used measure of interference control, did also fail to find interference control deficits,[4-5] suggesting that this type of inhibitory control may not be impaired in very preterm children. In this study described in Chapter 4,[6] we employed a stimulus-response compatibility task which did not yield switching impairments in very preterm children, consistent with earlier studies employing this paradigm.[3,6] Studies that have shown switching difficulties in this population with the Trail Making Test part B[2] may have reported biased switching effects since this task heavily draws on visual–spatial abilities that are frequently observed to be impaired in very preterm children.[7-8] **Chapter 5** showed that a sample of 50 early school-aged very preterm children (mean age = 5.9 years; SD = 0.4) born in 1998-1999 performed poorer than age-matched term children on measures of inhibitory control (i.e. prepotent response inhibition), switching, verbal working memory, verbal fluency, and conceptual reasoning. These deficits could not be explained by IQ nor by or processing speed, except for switching deficits. Switching skills in preschool were presumably so much immature that they were dominated by processing speed.[9-10] It has been questioned whether the Switch condition of the Shape School,[11] which was employed to measure switching in this study, 'constitutes a developmentally appropriate or reliable measure of set-shifting in preschoolers'.[10] The number of very preterm children that performed 1.0 SD below the term group mean was two to three times higher than for the term children.

Taken together, studies undertaken to answer the first research question and described in Chapters 4 and 5 postulate that executive dysfunction in very preterm children is not a global deficit, but rather constitutes a unique profile of affected and non-affected areas which remains largely consistent between 4.0 and 12.0 year and can be differentiated from impaired IQ and processing speed.

The second research question, i.e. what neonatal and social environmental factors are predictive for impaired EF in very preterm children, was addressed in **Chapters 5 and 6**. In **Chapter 5**, a composite score of neonatal risk was calculated with the neurobiological risk score (NBRS).[12] The NBRS summarizes neonatal medical events, with higher scores indicating a higher degree of neurobiological risk. The NBRS was regressed on EF performance of the small cohort of 50 very preterm children as described in one of the former paragraphs. The NBRS was not significantly predictive for impaired EF in very preterm children. Maternal education explained a significant proportion of 12% of the variance in EF in very preterm children (β = 0.31). **Chapter 6** regressed neonatal risk factors that were selected on the basis of the literature which included gestational age, birth weight standard deviation score, postnatal growth at 6 weeks corrected age, intra ventricular hemorrhage grade III and IV, oxygen dependency at 36 weeks postconceptional age, and the incidence of meningitis and necrotizing enterocolitis, separately, on EF in the large sample of 200 very preterm children as described in Chapter 3. Neonatal risk factors were, converging with the findings described in Chapter 5, not significantly associated with impaired EF, though a higher level of parental education was significantly associated with better EF ($\beta_s > 0.14$). A small but significant role was, however, found for degree of dysmaturity in predicting poor verbal working memory and fluency performance (β = 0.16) which converges with findings of studies on intelligence after very preterm birth.[13]

Taken together, studies undertaken to answer the second research question and described in Chapters 5 and 6 did not find convincing evidence that an adverse neonatal history is an important predictor for impaired EF in very preterm children. Neither a composite of neonatal risk nor isolated neonatal risk factors, such as intraventricular haemorrhage, chronic lung disease, or severe inflammatory diseases, were in our studies identified as crucial for impaired EF in very preterm children. Adverse neonatal circumstances have been related to the occurrence of disabilities or low IQ scores in very preterm infants,[14] but may not be suitable predictors of more 'subtle' neurocognitive functions such as EF. In contrast, we found, commensurate with earlier research,[15] that social factors, such as highly educated parents which may offer an optimal home environment, are important for better EF in very preterm children.

The third research question, i.e. what is the impact of impaired EF on academic achievement and behavior in very preterm children has been examined in **Chapter 7**. Effects of very preterm birth status, impaired processing speed (see Chapter 4), IQ, and EF, were regressed on mathematics and attention ratings which enabled to determine the unique contribution of each of these variables to mathematical and attention problems. Analyses were performed with the sample of 200 very preterm and 230 term children as described in Chapter 3. Contrasting earlier studies,[16-17] slow and highly variable processing speed was not significantly predictive for mathematical and attention problems. Effects of speed observed by earlier studies may be confounded, however, since speed measures were used of which psychometric properties have been questioned and which heavily rely on fine motor coordination,[18-19] a skill frequently observed to be impaired in very preterm children.[32-35] In our study, impaired EF and IQ scores were important predictors for poor mathematical achievement and attention problems in primary school in very preterm children. In particular lower IQ scores were found to be significantly related to poorer mathematical performance ($\beta_s > 0.16$), whereas both poorer EF and IQ scores were important predictors for increased rates of attention problems ($\beta_s > -0.18$). EF domains that were predictive for attention problems concerned spatial working memory/planning skills which were important for both parent and teacher ratings of inattention, and inhibitory control skills which were important for teacher rated attention problems, findings that converge with the literature.[20-22] The inconsistency between parent and teacher ratings in whether these are associated with EF task performance has been observed previously and has been explained by the fact that teachers may be more optimal informants for attention problems.[23-24] The impact of EF and IQ on attention problems was significantly stronger for very preterm children than for term children (interaction effect: $\beta s > -0.16$) which suggests a distinct neurocognitive basis for attention problems in very preterm children compared to term peers.[25] We did not find links between IQ, nor EF, and symptoms of inattention in preschool, which may be explained by the fact that inattentiveness in many normally developing young children reflects immaturity in behavioral adjustment, rather than a 'true' attention deficit in isolation.[26] The strong impact of IQ on mathematics in preschool and in primary school may be explained by the fact that our IQ estimate comprises for at least 50% visual-spatial skills (i.e. subtest Block Design) which have been identified as strong predictors for mathematical abilities.[27-28]

Taken together, the study undertaken to answer the third research question and described in the last but one chapter showed that deficits in mathematics and symptoms of inattention following very preterm birth are associated with impaired neurocognitive abilities expressed by weak IQ and EF performance but not with slow processing speed. Relationships between these indices of outcome on the one hand, and IQ and EF on the other hand, in preschool differed from those in primary school and interacted with very preterm birth status.

GENERAL DISCUSSION

Very preterm children that survived without severe disabilities are at great risk for substantial academic and behavior problems, of which deficits in mathematics and symptoms of inattention are most pronounced.[2, 29] These problems become apparent in the very beginning of preschool and remain existent throughout their entire primary school period.[29] This faltering academic and behavioral functioning was significantly related to impaired EF and IQ scores. Impaired EF in very preterm children was found to be associated with prenatal growth and level of parental education but not with neonatal complications. Involved EF sub-skills included inhibitory control (i.e. response inhibition), working memory, fluency, and planning. The impact of EF on mathematics in very preterm children was smaller than found in other studies on this subject (e.g.[16, 30]). A possible explanation may be that EF shares variance with IQ (e.g.[31]) and that in our study effects of EF were calculated whilst controlling for IQ, whereas in earlier studies effects of EF were compared to IQ. EF was found to become important as of the time children start attending primary schooling, and not just yet in preschool. A reason for this finding may be that in the preschool age, EF is presumed to be not yet as fractionated as in the middle school age (e.g.[32]). EF sub-skills develop at different rates[33] and may not even be fully matured in adolescence.[34-36] As (very preterm) children grow older, the environment becomes increasingly complex and demanding, appealing to a diverse set of EF sub-skills to function normally. Poor EF may hamper this ability to function normally.[14] In contrast to findings in earlier studies, we found processing speed was not to be significantly related to poor EF, nor to mathematical underachievement and attention problems in very preterm children.[30, 37] At closer inspection, the employed measures in these earlier studies showed that speed measures that had been used required a mental consideration, or depended heavily on fine-motor skills. Our studies, in contrast thereto, showed that a 'pure' speed measure, not reflecting any mental effort or fine-motor skill, was found to be slower in very preterm children, albeit not related to EF deficits or academic and behavior problems.

Our factor analysis revealed a structure of three factors within EF. The first factor consisted of verbal working memory/verbal fluency, the second factor spatial working memory/planning, and the third factor included inhibitory control indices. Assuming the presumption that verbal fluency substantially loads on the working memory system,[38] and that planning abilities have been proven to depend on working memory and inhibitory control activity,[39] then, our factor analysis, in fact, demonstrates that core executive problems in very preterm children encompass limited working memory accompanied by impaired inhibitory control skills. This fractionation of EF sub-skills converges with theories stating that the interaction between working memory and inhibitory control is fundamental to EF.[40-44] In very preterm children, it is than the limited capacity to temporarily maintain and manipulate information (i.e. working memory) as well as an impaired ability to handle conflicting information subsequently failing to suppress inappropriate responses (i.e. inhibitory control) that may cause a cascade of further EF deficits.[45]

We have demonstrated in this thesis that attention problems in very preterm children was not explained by impaired processing speed, but rather by impairments in spatial working memory and inhibitory control skills. These observed relationships between inattention and working memory confirm findings of earlier studies,[16-17] however, the significant effects of diverse aspects of inhibitory control on inattention in very preterm children is new. Earlier studies[16] related the number of inhibitory errors to attention problems and did not find significant relationships. Differences our findings and those of earlier studies may be caused by a number of factors, such as differences in measures employed, sample size studied, and choice of dependent variables related to attention problems. Nevertheless, findings should be compared with caution since there are up to now very few studies conducted on this subject and drawing conclusions on the exact nature of attention problems in this population remains delicate. Certainly more studies are needed on the effects of slowed and variable responding and aspects of inhibitory control on attention problems after very preterm birth. Anyhow, our task of inhibitory control (i.e. stop signal task) reflects diverse aspects of inhibitory control, namely the difficulty to stop a go-response (i.e. commission errors) as well as the latency needed to stop a no-go response (i.e. stop signal reaction time). Such a measurement of response inhibition provides an elegant insight in the covert processes underlying inhibitory control in very preterm children's.[46] Very preterm children not only performed substantially slower and more variable than term children on this task, but also displayed significant difficulties with inhibiting the go-response as well as with the no-go response. Thus, once a go-response has been started, very preterm children have great difficulties with stopping this response, a deficit which was subsequently found to be a strong predictor of symptoms of inattention in these children. Interesting to note is that such impairments are also observed in children diagnosed with ADHD inattentive subtype as well as with hyperactive/impulsive subtype. However, though very preterm children are generally rated as inattentive and easily distractible,[2] studies report mixed findings on whether these children are rated as being impulsive or overactive.[2] In addition, they generally do not fail on typical interference control measures.[4-6] Taken these thoughts and our findings together, it may be suggested that attention problems in very preterm children are not as such related to an underlying increased sensitivity to distracting stimuli, but rather represent these children's limited capacity to handle a body of conflicting information and failure to organize their behavior and suppress inappropriate responses. It may be carefully concluded that it is thus not speed with which information of different modalities is processed across the brain, but rather the limited power or capacity to integrate, manipulate, and regulate, these diverse modalities to come to appropriate and meaningful behavior which seems to be the constraining factor in very preterm children. Supportive for this line of thought are recent meta-analytic studies on very preterm children's visuo-motor integration skills and complex language skills[47] that demonstrate that very preterm children generally perform normal on 'simple' tasks, however fail once more 'complex' tasks need to be performed.

In conclusion, findings of the studies described in this thesis showed that (please see FIGURE 1):

1) very preterm children are at high risk for time-persisting adverse academic and behavioral sequelae with the most prominent areas of dysfunction being mathematics and attention.

2) poor EF in very preterm children is not a global deficit but rather comprises of affected and non-affected areas of functioning.

3) EF in very preterm children is not as much predicted by adverse neonatal circumstances as it is by a high level of parental education.

4) not impaired speed with which information of different modalities is processed across the brain, but rather impaired IQ and EF performance were predictive for poor mathematical achievement and attention problems in very preterm children.

Limitations

The studies comprehended in this thesis also have their limitations and can be criticized on a number of issues. Our use of the Dutch Pupil Monitoring System[1] to measure academic achievement may raise questions on the heterogeneity of findings, since tests were administered on a diverse range of schools. However, the unique features of this pupil monitoring system resulted in a total of 95% of the Dutch schools using this

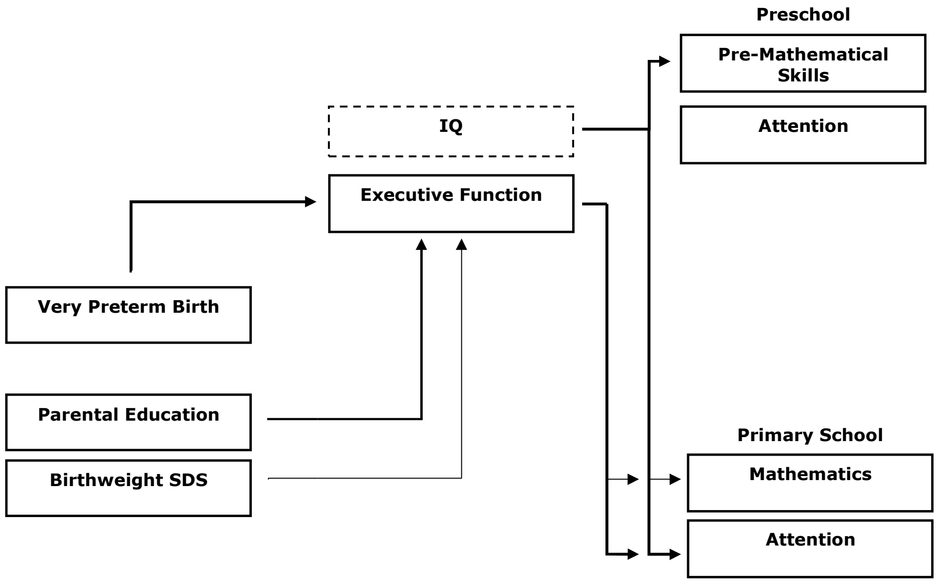


FIGURE 1 Main Findings of This Thesis

The thickness of the lines represents the strength of the relationship

system. These features include standardized tests that have been specifically developed and validated to monitor pupils' development in relation to both individual and peer development at a given time during the school year and throughout ongoing development.[1] Another limitation of our study design is that although the term born controls were recruited from the same schools as the very preterm children attended to control for educational environmental characteristics, the level of parental education was high in the comparison group, possibly because highly educated parents are more willing to participate. It may have been better to have matched classmates on age, gender, parent educational level, and IQ. A different important limitation is the lack of longitudinal data which would have enabled to calculate growth patterns of academic achievement, behavior, and EF, and also to calculate whether EF deficits may effectively antecede academic and behavior problems in very preterm children. Reliability and validity have not been fully assessed for all of our measures. However, the measures concerned have all been adopted from well-established paradigms which have been found fruitful in elucidating functioning of brain regions associated with EF functioning such as the corpus callosum, the cerebellum, the cingulate gyrus, and the prefrontal cortex.[48-53] Assessment of neonatal risk factors and the use of parental education as an index for social environmental circumstances was restricted and must therefore be mentioned as another limitation, because we may have underestimated the true contribution of biomedical risk on the development of the brains of very preterm children for these factors have been proven to be influential on very preterm children's outcomes.[54] Other prenatal factors associated with preterm birth, such as maternal nutritional status, pregnancy history, infections, uterine contractions, biological and genetic markers,[55] but also maternal smoking,[56] and alcohol consumption,[57-58] may impact white and gray matter development and subsequently executive functioning of very preterm children. Postnatal conditions ranging from experienced stressors in the neonatal ward[59] to parent-infant bonding[60-61] may also have had differential effects on the development of executive function in this population. In addition, we did not examine the contribution of more proximal indices of social environmental circumstances such as neighborhood, presence of resources, opportunities to engage in sports or hobbies, which may, as very preterm children grow older, positively contribute to EF.[62] These limitations warrant for future possible studies.

Implications for neonatal follow-up care

EF may be used to identify those children at risk for mathematical deficits and attention problems. This implies that neonatal follow-up care should expand their conventional IQ assessments with EF assessments. Exclusive assessment of IQ does not sufficiently capture the full range of executive abilities that underlie academic and behavioral problems. This set of neurocognitive functions should be employed as 'purely' as possible isolating one single aspect of EF, using tests that have been selected to minimally appeal to fine-motor skills and processing speed. In addition, given the continued rapid development up to young adulthood of (pre)frontal cortex subserving EF,[35,63-64] long-term longitudinal care is needed following up children born very preterm after discharge from the hospital throughout their school career, in order to identify and monitor those children in need for support.

Directions for future research

While our findings have added a piece to the puzzle of very preterm children's academic and behavioral function and the impact of EF on these areas of functioning, they have also raised a number of important and interesting new themes for future research. The first theme concerns the further clarification of EF in very preterm children, the second theme relates to the further study of mechanisms or pathology underlying academic and behavioral difficulties as well as impaired EF in very preterm children, with lays an important foundation for the third theme which is the further examination of predictors of academic and behavioral functioning after very preterm birth. A fourth and final important theme to be addressed by future possible research is the study of possibilities for intervention.

First, given our generated hypothesis on our findings being that working memory and inhibitory control form the core executive deficits in very preterm children, future studies could further investigate whether this hierarchical model of EF development holds true for children born very preterm. Such a model would incorporate fractionated developmental trajectories of EF sub-skills and could propose that the maturation of one EF sub-skill is essential for the maturation of a later developed EF sub-skill.[45] For instance, Barkley's theory postulates that inhibitory control mastery is necessary for the development of working memory.[43] To examine such a paradigm, future studies may employ measures that tap into a comprehensive range of EF sub-skills with differing levels of complexity in which the degree of executive load is manipulated. Such a measure may commence with a control condition, followed by a range of experimental conditions in which the specific inhibitory, working memory, and interactions between both EF areas that sub-serve more complex executive skills, can be manipulated. The additional 'costs' in reaction time, delay, or accuracy, may serve as an index of the child's mastery in the concerning sub-skill assessed (for examples see [65-66]).

A second important theme regards the further study of pathology underlying academic and behavioral difficulties and poor EF in very preterm children. For example, the nature of attention problems in very preterm children in preschool may be further clarified. Inattention in very preterm preschoolers concerns a major problem.[67-69] Parent and teacher ratings in our study were 0.7 SD to 0.9 SD higher than for term children, but its nature seems different from inattention in primary school since it is not related to poor neurocognitive function. Recent event-related-potential studies have shown that early school-aged very preterm children may have altered processing of auditory stimuli and may be less flexible in utilizing attention strategies than term counterparts which may resulted in greater efforts to achieve similar levels of attention.[70-72]

In addition, future research could study brain abnormalities underpinning observed impairments in speed and EF in very preterm children. With respect to the slow and high variability in speed, it is likely that white matter disruptions affect efficiency of neural signalling, which in turn manifests in poor and highly variable task performance.[73] Such slow and fluctuating speed may, however, also have a energetic basis, i.e., reflecting under arousal and unstable arousal, which results from impaired sub-cortical functioning.[74] Furthermore, only a handful of studies has been conducted on brain abnormalities underlying executive dysfunction after very preterm birth. These studies nevertheless show that moderate to severe white matter abnormalities and grey matter volume loss are related to impaired EF.[52,75-77] Nosarti et al. (2008) found that these brain abnormalities were more predictive for EF scores than group membership (very preterm or term control) and suggest that such brain abnormalities thus 'could be used as a clinical marker for the identification of those individuals at increased risk for cognitive impairment, at whom targeted interventions could be directed'.[52] This calls for the search for a ‘neonatal image phenotype’ which has recently been identified for very preterm children’s poor developmental outcomes at 2 years.[78] EF sub-skills such a inhibitory control and working memory have been shown to elicit activation across distinct brain areas[79], an issue not examined yet in very preterm children.

A third theme that may receive attention in future research is the further examination of predictors of academic and behavioral functioning after very preterm birth. For instance this could encompass an expansion of the assessed array of neurocognitive and psychosocial areas of functioning presumed to be predictive for adverse academic and behavioral functioning. Recent studies showed that, for instance, phonological abilities, or visual-spatial processing, are of great importance in the prediction of mathematical and reading attainment.[25,80] Furthermore, there is a scarcity of studies that investigated relationships between protective proximal predictors of academic and behavioral functioning in very preterm children, such as neighborhood, presence of resources, opportunities to engage in sports or hobbies, or harming proximal predictors such as family adversity.[17] At the same time but on another level our control of statistical techniques specifically designed to predict future functioning should be improved. Contrasting to the practice in other fields of science, such as physics, the majority of presently published medical and developmental pediatric papers present their results on the basis of (multiple) regression techniques. However, for instance receiver operating characteristic curves, which enable the evaluation of diagnostic performances of a test or variable in predicting outcomes, may be a more precise and therefore preferred technique.[14] In addition, if studying longitudinal growth trajectories of functioning following very preterm birth that involve repeated measurements, then path analysis, structural equation modeling, and growth curve analyses may be more suitable than the presently used statistical techniques.[14]

A final important theme is the development of intervention programmes or therapies directed at specific improvement of EF in very preterm children at early ages. These intervention techniques may for instance range from improvements on the neonatal ward to try to minimize the risk for brain damage, to create optimal home environments for these children to reduce some of the long-term burden of very preterm birth. Efficacy and feasibility of infant intervention programs that directly grasp on improvements in neurocognitive and motor skills in very preterm children have yet been scarcely examined. Given the rising body of studies supporting the fact that visual-motor functions impact on academic achievement in very preterm children, it may be interesting to train these visuo-motor skills in this population.[81] With regards to EF, *Science* has recently published a full edition on EF therapies which highlights the weight of this theme.[82] Diverse methods described include computerized training programs, sports or aerobic exercises, and adjusted classroom curricula.[62] Klingberg and colleagues have presented behavioral and neurophysiological evidence in children that, for instance, working memory capacity can be enhanced by computerized training and that training effects also generalize to non-trained tasks requiring working memory capacity.[83-85] Sports may stimulate EF since it practises attention regulation, working memory, and planning.[62] In addition, it has been suggested to improve brain functioning in terms of increasing dopamine signaling, and broadening of neural networks. A recent study, for instance, demonstrated positive effects of aerobic fitness on EF. Increased childhood aerobic fitness was associated with greater dorsal striatal volumes which was in turn related to better performance on inhibitory control tasks.[86] Adjusted classroom curricula include 'Tools of Mind' which concerns a preschool and kindergarten program based on the essence of social pretend play. During pretend play, children must inhibit acting out of character (i.e. inhibitory control), remember their own and others' roles (i.e. working memory), and flexibly adjust as their friends improvise (i.e. cognitive flexibility/fluency).[62] There are also a number of practical guides available to teach executive skills in very preterm children.[87-88] Given the importance of level of parental education for EF in very preterm children,[9,89] which indicates that very preterm children take advantage of an intellectual environment in which early problem solving skills are stimulated, we expect that such stimulating efforts may be in particular successful in helping less advantaged very preterm children overcome their EF difficulties. In a large scale study assessing a cohort of 1,000 children from birth to the age of 32 years, it was demonstrated that children's' 'self-control', a covering term for what in this thesis is EF, can be distinguished from children's intelligence, social class, and home situation of their families.[90] Improvements in these self-control or executive processes were shown to be time persistent[90] which creates opportunities to interfere in the cascade of very preterm birth and its long-term academic and behavioral consequences.

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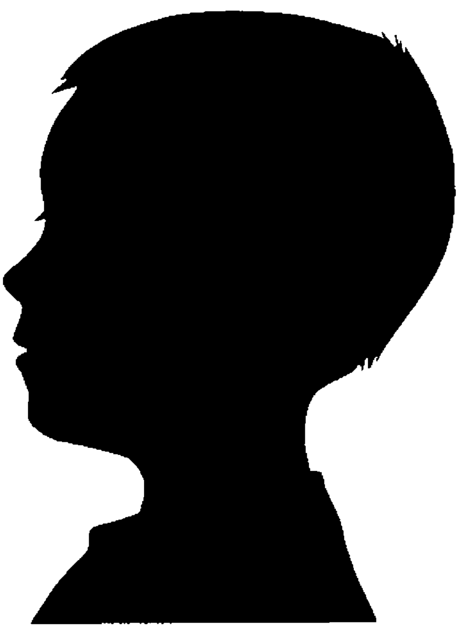
Chapter 9

Appendices



Samenvatting van de bevindingen

SAMENVATTING VAN DE BEVINDINGEN

De doelstelling van dit onderzoeksproject was om een gedetailleerd beeld van het executief functioneren (EF) van zeer te vroeg geboren kinderen (zwangerschapsduur < 30 weken) van 4.0 tot en met 12.0 jaar te verkrijgen. Tevens werd onderzocht welke neonatale en sociale omgevingsfactoren voorspellend zijn voor zwak EF bij zeer te vroeg geboren kinderen en wat het effect is van EF op schoolprestaties en gedrag van zeer te vroeg geboren kinderen.

Onderstaande alinea's vatten de bevindingen van de afzonderlijke studies, opgezet om deze doelstelling te behalen, samen. Na deze samenvatting zullen de belangrijkste bevindingen worden bediscussieerd in het licht van hoe zij onze kennis over EF en hun effect op schoolprestaties en gedrag van zeer vroeg geboren kinderen aanscherpen. Ten laatste zullen enkele beperkingen van dit onderzoeksproject worden besproken waarna afgerond wordt met aanbevelingen voor de neonatale follow-up zorg en vervolgonderzoek.

De eerste twee hoofdstukken beschrijven een uitgebreid literatuuronderzoek (Hoofdstuk 2) naar schoolprestaties, het gedrag, en EF, van zeer te vroeg geboren kinderen, en een diepgaande empirische studie (Hoofdstuk 3) naar schoolprestaties van zeer te vroeg geboren kinderen in vergelijking met à terme leeftijdgenoten.

In **Hoofdstuk 2** wordt een overzicht gegeven van alle studies naar schoolprestaties, gedrag en EF bij zeer te vroeg geboren (zwangerschapsduur < 33 weken in dit geval) kinderen en kinderen met een zeer laag geboortegewicht (VLBW: geboortegewicht < 1500 gram) gepubliceerd tussen 1998 en 2008 uit verschillende landen. Met behulp van meta-analytische technieken werd de ernst van de school- en gedragsproblemen en zwak EF van deze kinderen berekend. Zeer te vroeg geboren en VLBW kinderen scoorden gemiddeld 0.6 SD lager op rekentoetsen, 0.5 SD lager op leestoetsen, en 0.8 SD lager op spellingtoetsen dan à terme geboren (zwangerschapsduur > 37 weken) leeftijdsgenoten. De meta-analyse toonde verder aan dat aandachtsproblemen de meest ernstige vorm van gedragsproblemen betreft. Leerkrachten en ouders rapporteerden 0.4 SD tot 0.6 SD meer aandachtsproblemen voor deze kinderen dan voor hun à terme geboren leeftijdgenoten. Zeer te vroeg geboren en VLBW kinderen scoorden 0.4 SD tot 0.6 SD lager op verschillende EF testen. Deze ongunstige consequenties van de ernstige vroeggeboorte of het zeer lage geboortegewicht bleken voor te komen tot in de jonge volwassenheid, gemeten tot en met 22.3 jaar).

Hoofdstuk 3 beschrijft een diepgaande empirische studie naar de schoolprestaties van zeer te vroeg geboren kinderen. Tweehonderd zeer te vroeg geboren kinderen (gemiddelde leeftijd 8.2 jaar; SD = 2.5 jaar) geboren in de jaren 1996 tot en met 2004 zonder ernstige handicaps werden vergeleken met 230 à terme geboren kinderen (gemiddelde leeftijd 8.3 jaar; SD = 2.3 jaar) van vergelijkbare leeftijd en geslacht. Het Nederlandse CITO Leerling Volg Systeem werd gebruikt om schoolprestaties te meten. In groep 1 en 2 bleken zeer te vroeg geboren kinderen vergelijkbaar met à terme geboren leeftijdgenoten te presteren op de toetsen Taal voor Kleuters (i.e. taalontwikkeling), maar ze presteerden zwakker (0.7 SD) op de toetsen voor ordenen (i.e. voorbereidend rekenen). In groep 3 tot en met 8 presteerden zeer te vroeg geboren kinderen vergelijkbaar met de à terme leeftijdgenoten op toetsen voor begrijpend lezen en spellen, maar presteerden zwakker dan à terme leeftijdgenoten op toetsen voor technisch lezen (0.3 SD) en rekenen (0.6 SD). De prestaties op de eerste twee DMT kaarten (technische lezen van eenvoudige woorden) van zeer te vroeg geboren kinderen was in groep 3 en 4 zwakker dan die van hun à terme leeftijdgenoten, echter vanaf groep 5 was er geen significant verschil meer tussen beide groepen op deze toetsen. Zeer te vroeg geboren kinderen bleven echter gedurende de gehele basisschoolperiode zwakker presteren op de DMT kaart 3 (technische lezen van complexe woorden) en de toetsen voor rekenen. Zeer te vroeg geboren kinderen doubleerden vaak (25.5%), echter de kinderen die waren blijven zitten presteerden niet beter dan de zeer te vroeg geboren kinderen die niet gedoubleerd hadden. Daarom dienen andere methoden te worden onderzocht om de zwakke schoolprestaties van vroeg geboren kinderen te verbeteren.

De eerste onderzoeksvraag, welke zich richtte op het profiel van sterke en zwakke EF vaardigheden van zeer te vroeg geboren kinderen en de mate waarin dit profiel blijft bestaan van 4.0 to 12.0 jaar, werd onderzocht in de **Hoofdstukken 4 en 5**. **Hoofdstuk 4** beschrijft het onderzoek naar een uitgebreid scala aan EF, waaronder inhibitie (i.e. inhibitie van een dominante response en interferentie controle), verbaal en spatieel werkgeheugen, verbale vlotheid, flexibel schakelen en plannen, in het grote cohort van zeer te vroeg geboren kinderen. De karakteristieken van dit cohort zijn uitgebreid beschreven in Hoofdstuk 3. De resultaten toonden aan dat zwak EF bij deze kinderen een blijvend probleem is. Alleen de vaardigheid inhibitie van een dominante respons verbeterde naarmate deze kinderen ouder werden zodanig dat ze op 12-jarige leeftijd vergelijkbaar presteerden met de à terme controlegroep. Stoornissen in werkgeheugen (0.3 SD), verbale vlotheid (0.5 SD) en planning (0.4 SD) waren persisterend of bleven bestaan. Deze executieve defecten werden niet veroorzaakt door de tragere en inconsistente informatieverwerking van zeer te vroeg geboren kinderen, nog door het lagere IQ. De resultaten dragen bij aan de tot nu gepubliceerde studies over dit onderwerp, aangezien in deze eerdere studies geen onderzoek gedaan werd naar de persistentie van EF problemen en de samenhang tussen EF en snelheid van informatieverwerking bij zeer te vroeg geboren kinderen.

Belangrijk was de bevinding dat de zeer te vroeg geborenen niet zwakker presteerden op de testen voor interferentie controle en flexibel schakelen. Eerdere studies welke de Stroop test gebruikten, een veelgebruikte test voor interferentie controle, vonden eveneens geen interferentie controle stoornissen bij zeer te vroeg geboren kinderen, wat suggereert dat dit type inhibitie niet is aangedaan bij deze kinderen. Flexibel schakelen, gemeten met een klassieke stimulus-response compatibiliteitstest, was niet zwakker ontwikkeld bij de te vroeg geboren kinderen dan bij de à terme leeftijdgenoten, hetgeen consistent is met eerdere studies bij deze kinderen welke dit paradigma gebruikten.[3, 6] Studies die defecten met flexibel schakelen aantoonden bij zeer te vroeg geboren kinderen hanteerden de Trail Making Test deel B.· Echter, de door deze studies aangetoonde flexibel schakel defecten zijn mogelijkerwijs niet zuiver, aangezien de Trail Making Test een groot beroep doet op visueel-ruimtelijke vaardigheden welke zwakker zijn ontwikkeld bij zeer te vroeg geboren kinderen. **Hoofdstuk 5** onderzocht een uitgebreid scala aan executieve functies in 50 zeer te vroeg geboren (zwangerschapsduur < 30 weken) kinderen (gemiddelde leeftijd = 5.9 jaar; SD = 0.4 jaar) geboren in 1998-1999 en 50 op leeftijd gematchte à terme geboren kinderen (zwangerschapsduur > 37 weken. De resultaten toonden aan dat de groep zeer te vroeg geboren kinderen op de kleuterleeftijd zwakker presteerden dan de à terme kinderen op testen voor inhibitie, flexibel schakelen, verbaal werkgeheugen, verbale vlotheid en conceptueel redeneren. Deze stoornissen werden niet verklaard door zwakker IQ of snelheid van informatieverwerking, uitgezonderd de stoornissen in flexibel schakelen. De vaardigheid om flexibel te schakelen was waarschijnlijk nog zo onrijp dat deze bijna geheel gedomineerd werd door snelheid van informatieverwerking. Het is tevens de vraag of de Switch conditie van de Shape School waarmee de vaardigheid flexibel schakelen in deze studie werd gemeten, wel een 'geschikte en betrouwbare maat is voor flexibel schakelen bij kleuters'. Twee tot drie keer zo veel zeer te vroeg geboren kinderen presteerden 1.0 SD onder het gemiddelde van de à terme controlegroep.

Samengevat, de studies beschreven in de Hoofdstukken 4 en 5 brengen naar voren dat van executief disfunctioneren bij zeer te vroeg geboren kinderen een profiel gemaakt kan worden met zwak en op gemiddeld niveau ontwikkelde executieve deelvaardigheden welke constant blijft in de tijd en niet verklaard kan worden door IQ en snelheid van informatieverwerking.

De tweede onderzoeksvraag, die luidde welke neonatale en sociale omgevingsfactoren voorspellend zijn voor zwak EF van zeer te vroeg geboren kinderen werd behandeld in de **Hoofdstukken 5 en 6**. In **Hoofdstuk 5** werd een samengestelde score van neonataal risico berekend met behulp van de neurobiological risk score (NBRS). De NBRS vat neonatale feiten/complicaties samen waarbij een hogere score een hogere mate van neonatale ziekte en dus een hoger neurobiologisch risico indiceert. De NBRS werd gerelateerd aan EF van het kleine cohort van 50 zeer te vroeg geboren kinderen in de kleuterleeftijd zoals beschreven in de één na vorige alinea. De NBRS was niet significant voorspellend voor zwak EF in zeer vroeg geboren kinderen. Het opleidingsniveau van moeder, daarentegen, voorspelde 12% van de variantie in EF. **Hoofdstuk 6** relateerde neonatale risicofactoren welke geselecteerd waren op basis van de literatuur, te weten zwangerschapsduur, mate van dysmaturiteit, postnatale groei op 6 weken gecorrigeerde leeftijd, intra ventriculaire bloedingen graad III en IV, zuurstofbehoefte op 36 weken postconceptionele leeftijd, en de incidentie van meningitis en necrotiserende enterocolitis, aan EF in het grote cohort van 200 zeer te vroeg geboren kinderen zoals beschreven in Hoofdstuk 3. Neonatale risicofactoren waren, overeenkomend met de bevindingen in Hoofdstuk 5, niet significant gerelateerd aan EF bij de zeer te vroeg geboren kinderen. Een kleine, maar significante rol werd gevonden voor de mate van dysmaturiteit. Een hogere mate van dysmaturiteit hing samen met een zwakkere prestatie op de verbale werkgeheugen en verbale vlotheidstaken, hetgeen overeenkwam met studies waarin een dergelijk verband met intelligentie werd gevonden. Opnieuw werd wel een significant verband gevonden met opleidingsniveau van ouders, waarbij een hoger opleidingsniveau betere EF voorspelde.

Samengevat, noch een samengestelde neonatale risicoscore, noch neonatale risicofactoren afzonderlijk, zoals extreme prematuriteit of incidentie van longproblemen of inflammaties, waren in onze studies significant voorspellend voor EF bij zeer te vroeg geboren kinderen. Ongunstige neonatale omstandigheden kunnen voorspellend zijn voor het ontstaan van handicaps of mental retardatie, maar zijn wellicht geen geschikte voorspellers voor meer ‘subtiele’ neurocognitieve functies zoals EF. In tegenstelling, overeenkomend met eerder onderzoek, sociale omgevingsfactoren zoals een hoog opleidingsniveau van ouders, welke indicatief is voor een optimale thuisomgeving, werden belangrijk bevonden voor EF van zeer te vroeg geboren kinderen.

De derde onderzoeksvraag, welke luidde wat is het effect van zwakke EF op schoolprestaties en gedrag van zeer te vroeg geboren kinderen werd onderzocht in **Hoofdstuk 7**. De factoren vroeggeboorte, informatieverwerkingsproblemen (zie Hoofdstuk 4), IQ, en EF werden afzonderlijk gerelateerd aan zwakke rekenprestaties en aandachtsproblemen. De analyses werden uitgevoerd met het grote cohort van 200 zeer vroeg geboren kinderen en de controlegroep van 230 à terme geboren kinderen zoals beschreven in Hoofdstuk 3. In tegenstelling tot eerdere studies, waren informatieverwerkingsproblemen niet significant voorspellend voor zwak rekenen en aandachtsproblemen. De effecten van informatieverwerking zoals gevonden in deze eerdere studies zijn mogelijk niet zuiver aangezien snelheid van informatieverwerking was afgeleid van testen waarvan de betrouwbaarheid en validiteit betwijfeld kan worden. Ook doen deze testen een groot beroep op fijne motoriek (papier en potlood) welke vaak zwak is ontwikkeld bij zeer te vroeg geboren kinderen. In onze studie waren zwak EF en IQ belangrijke voorspellers voor zwak rekenen en aandachtsproblemen. Lagere IQ scores waren significant voorspellend voor zwakkere rekenprestaties, een zeer sterk verband werd gevonden met voorbereidend rekenen in groep 1 en 2. In groep 3 tot en met 8 was met name een zwak IQ significant geassocieerd met zwak rekenen, en zwak EF met aandachtsproblemen**.** Betrokken zwakke executieve deelvaardigheden waren spatieel werkgeheugen en inhibitie. Tevens was er een significant verband tussen een hogere mate van door de leerkracht gerapporteerde aandachtsproblemen en zwakke inhibitie. De inconsistentie tussen de relaties van door ouders of leerkracht gerapporteerde aandachtsproblemen en EF werd eerder ook gevonden en kan verklaard worden door het feit dat leerkrachten over het algemeen betrouwbaardere informanten van aandachtsproblemen zijn.

De invloed van EF en IQ op aandachtsproblemen was significant sterker bij de zeer te vroeg geboren kinderen dan bij de à terme kinderen, hetgeen mogelijk wijst op een verschillend in neurocognitieve basis voor de aandachtsproblemen bij de zeer te vroeg geboren kinderen in vergelijking met de à terme geboren kinderen. In dit proefschrift werd geen verband gevonden tussen EF of IQ en aandachtsproblemen in de kleuterklassen. Deze bevinding kan verklaard worden door het feit dat onoplettendheid bij kleuters onrijp gedrag reflecteert in plaats van zuivere aandachtstekortstoornissen. De sterke invloed van IQ op zowel het voorbereidend rekenen in de kleuterklassen als op rekenen in de hogere basisschoolklassen werd in dit hoofdstuk verklaard door het feit dat onze maat voor IQ grotendeels het visueel-ruimtelijke vermogen weerspiegelt (dit is de subtest Blokpatronen) welke een belangrijke voorspeller is voor rekenvaardigheden.

Samengevat, de laatste studie uitgevoerd om de derde onderzoeksvraag te beantwoorden toonde aan dat zwakke IQ en EF prestaties significant geassocieerd worden met zwak rekenen en aandachtsproblemen bij zeer te vroeg geboren kinderen. De tragere snelheid van informatieverwerking van de te vroeg geboren kinderen speelde geen significante rol. De verbanden tussen de neurocognitieve domeinen IQ en EF en schoolprestaties en gedrag verschilden tussen de kleuters en de oudere kinderen en verschilden tussen de zeer te vroeg geboren en de à terme geboren kinderen.

ALGEMENE DISCUSSIE

Zeer te vroeg geboren kinderen die geen ernstige handicaps aan de vroeggeboorte overhouden hebben een verhoogde kans om zwakke schoolprestaties en gedragsproblemen te ontwikkelen. Rekenproblemen en aandachtsproblemen zijn de meest ernstige vormen hiervan. Deze problemen worden zichtbaar op de kleuterleeftijd en blijven bestaan tot aan het einde van de lagere school. Deze haperende schoolprestaties en gedragsproblemen waren significant geassocieerd met zwakker EF en IQ. Binnen de groep te vroeg geboren kinderen bleek overigens een ernstigere mate van dysmaturiteit geassocieerd te zijn met zwakker EF. Een hoger opleidingsniveau van ouders bleek echter geassocieerd te zijn met sterker EF.

Executieve vaardigheden welke geassocieerd waren met reken- en aandachtsproblemen waren inhibitie en werkgeheugen. Het effect van EF op rekenen was kleiner dan in eerdere studies over dit onderwerp. Een mogelijke verklaring daarvoor is dat bepaalde EF deelvaardigheden ook gemeten worden door IQ testen, er is een gedeelde variantie. In onze studie is het effect van EF berekend terwijl gecorrigeerd werd voor het effect van IQ (waarbij dus een deel van het effect van EF weggevangen werd door IQ) terwijl in de eerder genoemde studies het effect van EF vergeleken werd met het effect van IQ. Het effect van EF op rekenen en aandacht werd gevonden voor de oudere kinderen, in groep 3 tot en met 8, en niet voor de kleuters. Een mogelijke verklaring voor deze bevinding is dat EF bij kleuters nog niet zo ver en gedifferentieerd is ontwikkeld als bij oudere kinderen. De verschillende EF deelvaardigheden ontwikkelen zich in een onderscheiden tempo bij kinderen en rijpen zelfs door tot in de jong volwassenheid. De omgeving wordt steeds complexer naarmate een kind ouder wordt en doet dan steeds meer beroep op een divers scala aan EF om 'normaal' te functioneren. Zwak EF kan dus naarmate zeer te vroeg geboren kinderen ouder worden steeds meer gaan belemmeren.

In tegenstelling tot eerdere studies over dit onderwerp, vonden wij in onze studie dat de trage snelheid van informatieverwerking van zeer te vroeg geboren kinderen niet verklarend was voor hun zwak EF, noch een verklaring was voor de gevonden relatie tussen EF en reken- en aandachtsproblemen. Nader bezien, deze eerdere studies gebruikten informatieverwerkingstesten waarbij of een bepaalde mentale beslissing 'in het hoofd' genomen moest worden of welke een sterk beroep deden op fijne motoriek. In onze studies, daarentegen, hanteerden we een naar onze mening zuiverdere test voor informatieverwerking welke enkel de snelheid van het reageren op een stimulus op het computerscherm weergeeft en geen inzet van fijn motorische vaardigheden vraagt. De factoranalyse van de executieve vaardigheden welke bij de zeer te vroeg geboren kinderen zwakker waren ontwikkeld dan bij de à terme geboren kinderen leverde een factorstructuur van drie afzonderlijke EF factoren op. De eerste factor bestond uit verbaal werkgeheugen en verbale vlotheid, de tweede factor bestond uit spatieel werkgeheugen en planning, en de derde factor bestond uit de maten voor inhibitie. Aangenomen de veronderstelling dat verbale vlotheid een substantieel beroep doet op het werkgeheugen systeem en het vermogen om te plannen sterk afhankelijk is van spatieel werkgeheugen en inhibitie dan zou de gevonden factorstructuur duiden op het feit dat EF problematiek bij zeer te vroeg geboren kinderen bepaald wordt door een zwak werkgeheugen en inhibitie problemen. Deze verdeling van EF deelvaardigheden correspondeert met theorieën dat de interactie tussen werkgeheugen en inhibitie fundamenteel is voor EF. Bij zeer te vroeg geboren kinderen is het dan de beperkte capaciteit om informatie tijdelijk te onthouden en te manipuleren (werkgeheugen) in combinatie met het zwakke vermogen om om te gaan met tegengestelde of tegenstrijdige informatie waarbij de inadequate reactie of gedrag onderdrukt moet worden (inhibitie) welke leidt tot een cascade van overige EF problemen.

Wat betreft de aandachtsproblemen bij zeer te vroeg geboren kinderen; in dit proefschrift werd aangetoond dat zwak IQ en EF, zoals spatieel werkgeheugen en inhibitie, sterk geassocieerd werden met deze aandachtsproblemen. Deze bevinding correspondeert met eerdere studies en vult deze studies aan, uitgezonderd het gevonden effect van inhibitie. Eerdere studies vonden geen significant verband tussen inhibitieproblemen en aandachtsproblemen, hetgeen te maken kan hebben met verschillen tussen de studies in de taken welke afgenomen zijn en het aantal kinderen waarop de statistische analyses uitgevoerd zijn. Aangezien het vergelijken van onze bevindingen met die van eerdere studies echter moeilijk is omdat er nog weinig studies zijn verschenen over de relatie tussen EF en aandachtsproblemen bij zeer te vroeg geboren kinderen is er dringend behoefte aan meer onderzoek naar deze relatie. Onze maat voor inhibitie reflecteert zowel het aantal keer dat een kind per ongeluk op de verkeerde knop drukte als de tijd die het kind nodig had om zijn of haar reactie te onderdrukken, wat een elegant inzicht biedt in de hersenprocessen onderliggend aan inhibitoire capaciteiten. Zeer te vroeg geboren kinderen drukten beduidend vaker per ongeluk op de knop en hadden significant meer tijd nodig om hun reactie te onderdrukken dan à terme geboren kinderen. Dit betekent dat als een reactie eenmaal is ingezet, zeer te vroeg geboren kinderen beduidend meer moeite hebben dan leeftijdgenoten om deze reactie weer te stoppen. In dit proefschrift werd tevens gevonden dat zeer te vroeg geboren kinderen snel afleidbaar zijn, maar niet zwakker presteren op interferentie controle taken. Als we deze bevinding samennemen met de hierboven beschreven relatie tussen werkgeheugen, inhibitie, en aandachtsproblemen, dan zouden we kunnen concluderen dat het aandachtsprobleem bij zeer te vroeg geboren kinderen niet zozeer bepaald wordt door een verhoogde gevoeligheid voor afleidende stimuli als wel door de beperkte capaciteit om (alle binnenkomende) informatie/stimuli te behandelen en op de juiste wijze te gebruiken, waardoor deze kinderen minder goed hun aandacht 'erbij' kunnen houden.

Samengevat, niet de snelheid waarmee informatie van verschillende modaliteiten wordt verwerkt is het probleem waardoor zeer te vroeg geboren kinderen vastlopen op school, maar veelmeer hun beperkte capaciteit om deze diverse informatie op de juiste wijze te integreren, manipuleren en reguleren. Anders gezegd, het gaat goed zolang relatief eenvoudige informatie uit bijvoorbeeld één modaliteit bediend moet worden, echter zeer te vroeg geboren kinderen gaan zwakker presteren wanneer informatie meerdere modaliteiten omvat (bijvoorbeeld visueel en motorisch) en complexe opdrachten gevraagd worden. Deze gedachte wordt ondersteund door recente meta-analyses over de visueel-motorische en talige vaardigheden van zeer te vroeg geboren kinderen waarin aangetoond werd dat te vroeg geboren kinderen gemiddeld presteerden op instrumenten voor simpele of eenvoudige vaardigheden, maar zwakker gingen presteren als de taak complexer werd.

Concluderend laten de studies in dit proefschrift zien dat:

1) zeer te vroeg geboren kinderen een verhoogd risico hebben om blijvende zwakke schoolprestaties en gedragsproblemen te ontwikkelen, waarvan rekenproblemen en aandachtsproblemen het meest opvallend zijn.

2) EF bij zeer te vroeg geboren kinderen niet volledig is aangedaan, maar er zijn zwak ontwikkelde ten opzichte van op gemiddeld niveau ontwikkelde deelvaardigheden te onderscheiden.

3) EF bij zeer te vroeg geboren kinderen niet zozeer voorspeld kan worden door ongunstige neonatale omstandigheden, maar veelmeer door het opleidingsniveau van de ouders.

4) niet de snelheid waarmee informatie van verschillende modaliteiten wordt verwerkt, maar zwak IQ en EF voorspellend zijn voor reken- en aandachtsproblemen bij zeer te vroeg geboren kinderen.

Beperkingen

De studies opgenomen in dit proefschrift waren onderhevig aan een aantal beperkingen. Zo resulteerde het gebruik van het CITO leerlingvolgsysteem in een heterogeniteit van scores vanwege de afname op verschillende scholen. Het voordeel echter van het gebruik van het CITO leerlingvolgsysteem was dat het door circa 95% van de Nederlandse scholen gebruikt wordt en dat het de mogelijkheid bood om de vorderingen van elke leerling ten opzichte van zichzelf, de klas, de school, en het landelijke gemiddelde te observeren. Wel waren er ontbrekende gegevens omdat scholen niet altijd hetzelfde beleid voeren met betrekking tot welke test wanneer afgenomen wordt. Een andere beperking was dat, ondanks dat de controlegroep op dezelfde scholen geworven was als welke bezocht werden door de zeer te vroeg geborenen, het opleidingsniveau van de ouders van de à terme controlekinderen beduidend hoger was dan dat van de zeer te vroeg geboren kinderen. Een goed alternatief zou zijn geweest om klasgenoten van gelijke leeftijd, geslacht en ouderlijk opleidingsniveau van de ouders als de zeer te vroeg geboren kinderen in de controlegroep te includeren. Verder, van sommige in dit proefschrift gebruikte instrumenten is de betrouwbaarheid en validiteit nog niet voldoende vastgesteld. Van deze instrumenten is echter wel bekend dat zij gebaseerd zijn op vastgestelde paradigma's en activiteit opwekken in de hersengebieden corpus callosum, het cerebellum, de gyrus cinguli en de prefrontaal cortex.

Ten slotte is de diversiteit aan onderzochte neonatale en sociale omgevingsfactoren enigszins gering waardoor de invloed van deze factoren mogelijkerwijs onderschat is. Prenatale factoren zoals voeding van de moeder, zwangerschapscomplicaties, infecties, biologische en genetische factoren, alsmede roken en alcoholgebruik van de moeder kunnen de witte en grijze stof in de hersenen van het kind hebben aangetast met gevolgen voor het EF van het kind. Evenzo zijn de effecten van postnatale stress en hechting tussen ouder en kind op EF in deze populatie niet onderzocht.

Betekenis van de bevindingen voor neonatale follow-up zorg

EF is nuttig gebleken in het voorspellen van reken- en aandachtsproblemen bij zeer te vroeg geboren kinderen en kan daarom worden gebruikt om kinderen te identificeren die een risico lopen op het ontwikkelen van reken- en aandachtsproblemen. Dit impliceert dat de neonatale follow-up zorg de gebruikelijke diagnostiek met behulp van IQ instrumenten zou kunnen uitbreiden met EF maten. Uitsluitend bepalen van het IQ van een kind is niet voldoende om de zwak ontwikkelde vaardigheden onderliggend aan reken- en aandachtsproblemen vast te leggen. Wel is het van belang dat EF zo zuiver mogelijk wordt gemeten met behulp van diagnostische instrumenten waarbij de EF score niet beïnvloed wordt door snelheid van informatieverwerking en welke geen beroep doen op fijne motoriek. Verder is, gezien de feit dat de prefrontaal cortex, een hersengebied waar EF met name 'zetelt', zich snel en tot in de jong volwassenheid ontwikkelt, lange termijn follow-up nodig om zeer te vroeg geboren kinderen na ontslag gedurende hun gehele schoolcarrière te kunnen vervolgen teneinde die kinderen met school- en gedragsproblemen tijdig te kunnen identificeren en de hulp te kunnen bieden waar ze recht op hebben.

Aanbevelingen voor toekomstig onderzoek

De bevindingen voorkoment uit dit onderzoek hebben een belangrijk ontbrekend stuk toegevoegd aan de puzzel van het ontstaan van zwakke schoolprestaties en gedragsproblemen bij zeer te vroeg geboren kinderen. Tegelijkertijd roepen zij nieuwe vragen op welke onderwerp zouden kunnen zijn van toekomstig onderzoek. Deze vragen beslaan onder meer de verdere opheldering van EF bij zeer te vroeg geboren kinderen. Op basis van de bevindingen werd verondersteld dt er mogelijkerwijs sprake is van een hiërarchisch model waarin werkgeheugen en inhibitieproblemen een hoofdrol spelen en leiden tot een cascade van andere EF problemen. Vervolgonderzoek zou een dergelijk model empirisch kunnen gaan toetsen met hulp van instrumenten waarin EF belasting gemanipuleerd wordt door deze bijvoorbeeld steeds verder te verhogen. Een tweede vraag waar toekomstig onderzoek zich op zou kunnen richten is het verder onderzoeken van pathologie onderliggend aan zwakke schoolprestaties en gedragsproblemen bij zeer te vroeg geboren kinderen. In de studies in dit proefschrift werd, bijvoorbeeld, geen verband gevonden tussen EF en aandachtsproblemen bij kinderen op de kleuterschool. Verder onderzoek zou zich kunnen richten op andere factoren welke bepalend zouden kunnen zijn voor aandachtsproblemen bij deze jonge zeer te vroeg geboren kinderen. Maar ook de basis van zwakke schoolprestaties en gedragsproblemen bij de oudere zeer te vroeg geboren kinderen dient verder onderzocht te worden. Voorbeelden van neurocognitieve factoren welke niet in dit proefschrift zijn onderzocht maar mogelijk wel van belang zijn, zijn fonologische en visueel-ruimtelijke vaardigheden. Ook hebben recente studies met à terme geboren kinderen laten zien dat meer distale factoren zoals het beoefenen van een sport of een hobby, de kwaliteit van het woongebied en gezinskenmerken van groot belang zijn voor goed EF. Tegelijkertijd dient dit soort predictie onderzoek zich te gaan bedienen van meer geavanceerde en nauwkeurigere statistische technieken, zoals path analysis, structural equation modeling, en growth modeling.

Een laatste belangrijke vraag waar toekomstig onderzoek zich op zou kunnen gaan richten is het ontwikkelen en valideren van interventieprogramma's welke gericht zijn op het trainen van neurocognitieve vaardigheden bij zeer te vroeg geboren kinderen. Deze interventieprogramma's kunnen bestaan uit medische interventies op de neonatale intensive care teneinde het brein van zeer te vroeg geboren kinderen te sparen, maar ook gedraggestuurde interventies om EF op de schoolleeftijd te verbeteren. Tot op heden zijn er nog geen publicaties bekend over het trainen van EF bij zeer te vroeg geboren kinderen. Wel zijn er studies verschenen, zie onder meer een recente uitgave van het tijdschrift *Science*, naar EF training bij à terme geboren kinderen met zeer positieve resultaten. Het trainen van geïdentificeerde neurocognitieve problemen biedt de mogelijkheid om de cascade van vroeggeboorte en daaropvolgende school- en gedragsproblemen te onderbreken.

Dankwoord

Dankwoord

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PhD Portfolio

PhD Portfolio

Names

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Courses	Year	Workload (Hours)
Biomedical English Writing and Communication, Rotterdam	2008	80
Nihes Course Classical Methods of Data-Analysis, Rotterdam	2005	160
Nihes Course Repeated Measurements, Rotterdam	2009	80
Structural Equation Modelling using AMOS©	2010	20

Oral Presentations

"*Executieve functies bij ex-prematuren op kleuterleeftijd*." Neonatale Neurologie, Amsterdam, The Netherlands	2006	20
"*Regulatie van gedrag en cognitie; over leer- en gedragsproblemen bij prematuur geboren kinderen*." Early Aid, Nijmegen, The Netherlands	2006	20
"*Lange termijn follow-up van zieke pasgeborenen om leer- en gedragsproblemen te voorkomen*." Circle of Life, Rotterdam, The Netherlands	2006	20
"Academic achievement, behavioural problems and executive function in very preterm and/or VLBW children: a meta-analysis." Landelijke Neonatale Follow-up Werkgroep, Utrecht, The Netherlands	2009	20
"*Leer- en gedragsproblemen bij het prematuur geboren kind op school, waar gaat het mis?"* Dutch Society Perinatal Medicine, Utrecht, The Netherlands	2009	20
"*IQ and executive functions predict mathematical and attention problems in very preterm children*." Pediatrische Psychologie Nederland, Nijmegen, The Netherlands	2011	20

Poster Presentations

"*Executive function in very preterm children and controls*." Development of Executive Function, Oxford, United Kingdom	2008	10
"*Meta-Analysis of neurobehavioral outcomes in very preterm and/or VLBW children."* European Society of Paediatric Research, Hamburg, Germany	2009	10

Lecturing		
Neuropsychological consequences of preterm birth. Graduate Course Child Neuropsychology, Leiden University, Leiden, The Netherlands	2008-present	28

Supervising Master's theses		
Any Haq. *Een onderzoek naar inhibitie bij ex-prematuren*.	2006	6 months
Baars, Marsha. *Executive function and attention among very preterm children.*	2007-2011	14* 6 months
Breunese, Anouk. *Examination of neonatal factors as predictors of poor executive functioning performance at school age in very preterm born children*.		
Haddad, Suzanne. *Motorische inhibitie bij prematuur geboren kinderen met en zonder Attention Deficit Hyperactivity Disorder (ADHD).*		
Meijer, Ingrid. *Developmental trajectory of inhibition and working memory in very preterm children.*		
Mous, Sabine. *Academic achievement in very preterm children: what are the problems and underlying deficits in executive functioning?*		
Nazila Quame. *Gedragsproblemen in prematuur geboren kinderen*.		
Rots-de Vries, Lisette. *The development of executive functions in relation to academic achievement in primary school aged very preterm children.*		
Rottier, Anne. *Socioeconomic status and executive function in very preterm born children aged 6 to 12 years.*		
Sandjojo, Janice. *The influence of neonatal risk factors on executive functioning in very preterm children.*		
Steekers, Anja. *The development of executive function in children born very preterm*.		
Verhage, Marije. *Leer- en gedragsproblemen bij prematuur geboren kinderen tussen 4 en 12 jaar.*		
Van Veen, Heske*. The influence of socioeconomic status on executive function in very preterm children at school age.*		
Van der Werf, Antoinette. *The male disadvantage; gender differences in cognitive functioning in premature and dysmature children in the age of 4-12 years*.		
Zwirs, Renate*. Inhibition in very preterm children: the developmental course during early and middle childhood.*		