Executive Function Assessment in 2-Year-Olds Born Preterm

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Abstract

Objective   Our objective was to investigate the executive function and its relationship with gestational age, sex, maternal education, and neurodevelopmental outcome at 2 years corrected age in children born preterm.

Method   Executive function was assessed by means of the Multisearch Multilocation Task (MSML), Reversed Categorization Task (RevCat), and Snack Delay Task (SDT). Infant and maternal characteristics were gathered from the child's record. The developmental outcome was measured by the Bayley Scales and a multidisciplinary risk evaluation for autism.

Results   The executive function battery was completed by 97 children. The majority were able to successfully complete the MSML and SDT but failed RevCat. The lower the gestational age and the maternal education, the lower the executive function scores. Better cognition and motor function, as well as low autism risk, were associated with better executive function scores. Executive function was not related to sex.

Interpretation   This cohort study provides evidence that it is feasible to assess executive function in 2-year-olds born preterm. Executive function is related to gestational age and maternal education and is positively correlated with behavioral outcome. Therefore, executive functions can be a valuable target for early intervention, resulting in improvements in neurodevelopmental outcomes in children born preterm.

Keywords
► executive function
► children born preterm
► neurodevelopment

Introduction

More than 10% of all babies are born preterm.[1] Advances in neonatal care have improved survival rates; however, children born preterm remain at risk for motor delays, behavioral problems, and cognitive impairments, including executive function (EF) deficits.[1,2] EF refers to higher-order, self-regulatory, cognitive processes including working memory, inhibitory control, and cognitive flexibility.[3] Working memory is the ability to mentally represent and manipulate information over short time intervals, inhibitory control refers to the capacity to suppress attention or responses to an irrelevant stimulus, and cognitive flexibility makes it possible to shift fluidly between different tasks.[4,5] At a neural level, EF skills are primarily hosted in the prefrontal cortex, a neural structure characterized by a late and prolonged maturation pattern.[4] Accordingly, EF skills start to develop toward the end of the first year of life.[4] First inhibitory control emerges, followed by working memory and cognitive flexibility.[3,6] As typical EF development depends on intact brain network connectivity, which is often compromised after preterm birth, it is reasonable to expect that preterm infants perform more poorly on EF.[2,7,8] A recent systematic review[9] and meta-analysis[2] confirmed

the presence of EF deficits in preterm children throughout development and demonstrated that they are most pronounced at preschool age.[9] In the youngest participants, at the age of 2 years, group differences in cognitive flexibility and working memory were demonstrated between preterm and full-term children,[10,11] with working memory deficits being associated with bilateral reductions in total brain volume[11] and altered hippocampal volume at discharge from hospital.[12] Thus far, however, few studies investigated the three major EF components in concert at this young age, and no study investigated the association between EF performance and infant and parent characteristics. Moreover, children with brain damage were often included in the preterm samples, making it difficult to draw strong conclusions about the specific effect of prematurity alone. Difficulties in EF have been suggested to play a key role in various neurodevelopmental disorders, including autism spectrum disorder (ASD),[13] attention deficit hyperactivity disorder (ADHD),[14] and specific learning disorders, such as arithmetic, reading, and spelling disorders,[15] all of which are overrepresented in the preterm population.[16] Importantly, EF difficulties have been shown to precede and predict impairments along these various neurodevelopmental domains.[2] Therefore, early identification of children at risk for EF difficulties is of great interest to enable early intervention and improvement in EF and subsequent neurodevelopmental outcomes.[2,17] Against this background, it is important to study EF as young as possible. However, research and clinical work on the early development of EF (deficits) have been limited until recent years by the lack of suitable measures.[18] Building on recent advancements, the aim of this paper is to investigate EF using a broader age-appropriate assessment battery in a homogeneous cohort of 2-year-old preterm born infants and describe the association with gestational age, sex, maternal education, and neurodevelopmental outcome measures.

Methods

Participants

Children born in the University Hospital Leuven between August 2016 and July 2018 were prospectively recruited at birth if they were born before 34 weeks gestational age (GA) and/or with a birth weight (BW) lower than 1,500 g. Parents were informed about the study in the first week after birth and asked for written consent. Exclusion criteria were (1) maternal age less than 18 years, (2) inability of both parents to speak and understand Dutch or English, (3) unstable medical disease in one of the parents, and (4) the presence of a major congenital malformation or major central nervous system pathology (grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia) in the preterm infant. The latter were excluded to allow studying a homogeneous cohort of preterm born children. The study has been approved by the Ethical Committee of the University Hospital Leuven and is performed in accordance with the Guidelines for Good Clinical Practice and the latest version of the Declaration of Helsinki. It has been registered at Clinical Trials.gov (NCT02623400).

Procedure

Birth characteristics of the infant, such as GA and BW, were retrieved from the child's record and are displayed in ►Table 1. As a reflection of socioeconomic status, maternal education was assessed according to the International Standard Classification of Education scale[19] by converting classifications on the original 7-point scale to a 2-point scale (lower/higher), with lower education referring to a maximal

Table 1 Participant characterization for the full patient sample, gestational age < 32 weeks, and gestational age ≥ 32 weeks

	Full sample (n = 97)	Gestational age <32 w (n = 63)	Gestational age ≥32 w (n = 34)	p-Value[a]
Gestational age (weeks), mean (SD)	30.1 (2.4)	28.9 (2.1)	32.5 (0.5)	<0.001
Birth weight (grams), mean (SD)	1396 (401)	1241 (375)	1682 (273)	<0.001
Mean age at 2-y testing Sex	24.4 (0.9)	24.3 (1.1)	24.6 (0.8)	0.147
Male, n (%)	63 (65)	41 (65)	22 (65)	0.971
Female, n (%)	34 (35)	22 (35)	12 (35)	
Maternal education				
Lower, n (%)	30 (31)	18 (29)	12 (35)	0.494
Higher, n (%)	67 (69)	45 (71)	22 (65)	
BSID-III cognition, mean (SD)	102 (20)	101 (24)	104 (11)	0.640
BSID-III language, mean (SD)	92 (23)	91 (27)	95 (12)	0.424
BSID-III motor function, mean (SD)	106 (16)	105 (18)	108 (10)	0.508
Individuals identified at ASD risk, n (%)	17 (18)	16 (25)	1 (3)	**0.006**

Abbreviations: ASD, autism spectrum disorder; BSID-III: Bayley scales of infant and toddler development III.
Note: Data presented in mean (SD) and n (%).
Note: Explanation: maternal educational level: lower = no degree, primary school, or secondary school; higher = bachelor's or master's degree.
[a]p-Values for GA group comparisons based on chi-square test or Mann–Whitney U test, p-values < 0.05 are presented in bold.

education up till high school and higher education implying that mothers obtained at least a bachelor degree. At 2 years corrected age, children attended the specialized local clinic (Center for Developmental Disorders, UZ Leuven) for a standardized neurodevelopmental assessment. The assessment included the EF battery, testing of motor, language, and cognitive abilities with the Bayley Scales of Infant and Toddler Development III (BSID-III)[20,21] and a multidisciplinary risk evaluation for ASD according to DSM-5 criteria (binarized as no risk [0] versus risk[1]).[22] The EF assessment took 15 minutes and was performed in the context of a global developmental assessment during the regular follow-up of these children. In total, the assessment lasted 4 hours and was conducted by a certified physiotherapist, psychologist, and pediatric physician. Regular breaks were provided for refreshment and play.

Executive Function Measurements
The EF battery was based on previous reports in preschool samples by Carlson and Ansell.[3,23,24] We adapted the tasks to make them more appealing for very young children and administered them according to a standardized protocol. In line with,[23] for each of the tasks, we determined a minimal score to consider the task performance as successful, that is, indicative of minimal mastering of the underlying cognitive ability.

Multisearch Multilocation Task (MSML). This task is a modified A-not-B task developed by Zelazo for use with toddlers.[25] In contrast to the original four-step MSML process applied by Zelazo and the three-step MSML process applied by Ansell,[3,26] here, we used a two-step process because motor demands were suspected to be too big for many 2-year-old preterm infants. In addition, we opted to use bright-colored boxes instead of boxes labeled with symbols, to simplify the task for children with suspected cerebral visual impairment. Three colored boxes were presented to the child: yellow, red, and blue. In the preswitch trial, a toy animal was placed in the red box. The child watched the toy animal being hidden and was encouraged to retrieve it. A trial was scored as successful if the child found the toy animal on the first attempt. Preswitch trials continued until the child achieved three consecutive correct trials or until four trials were attempted. One point was awarded for each correct attempt. The postswitch trial was introduced as a "silly game" and the child was encouraged to watch as the toy animal was now hidden in the yellow box. A 10-second delay was imposed before the child was presented with the boxes and encouraged to find the toy animal. The postswitch trials continued until the child had correctly searched on two consecutive trials or until six postswitch trials had been attempted. The postswitch trials were reverse scored with 6 points awarded for the first two searches both being correct, and thereafter penalizing for each error. As such, scores from preswitch searching ranged from 0 to 3 and postswitch searching from 0 to 6, giving a maximum MSML total score of 9 points. Achieving the maximum MSML total score was defined as MSML success.[3,23,25,26]

Reversed Categorization Task (RevCat). The RevCat was administered according to the guidelines by Carlson.[23] In the preswitch phase, the child was encouraged to put three yellow blocks in a yellow bucket and three blue blocks in a blue bucket. In a postswitch phase, the child was told to put three yellow blocks in the blue bucket and three blue blocks in the yellow bucket. One point was awarded for each block correctly sorted. To determine the total score, children were allocated to groups based on the highest level they achieved, with the following possible outcomes: (1) preswitch score less than 5 and postswitch score less than 5, (2) minimum preswitch score of 5 and postswitch score less than 5, (3) minimum preswitch score of 5 and postswitch score of 5, (4) minimum preswitch score of 5 and postswitch score of 6. Three points were given for outcome 4, 2 points for outcome 3, 1 point for outcome 2, and 0 points for outcome 1, yielding a maximum RevCat total score of 3 points. RevCat success was defined as a minimum preswitch and postswitch score of 5, that is, a score of 2 points.[3,25]

Snack Delay Task (SDT). This task was developed by Kochanska et al (2000) but was adjusted to three trials instead of four.[27] A biscuit was placed in front of the child, on a plate underneath a transparent upturned glass. The experimenter had a bell in front of her, on the same table. The child was instructed to wait for the bell to be rung before retrieving the treat. Three consecutive trials with a delay of 5, 15, and 30 seconds were performed. Waiting for the ringing of the bell before touching and retrieving the treat was scored as a full wait, while lifting or touching the glass without eating the treat was defined as a partial wait. Eating the treat or ringing the bell by the child prior to the bell being rung by the experimenter was defined as a failed trial. The assessment continued until all three trials were completed or until the first failed trial. SDT total score was the number of trials with a full wait. Accordingly, SDT total score ranged from 0 to 3. SDT success was defined as a full wait for at least 5 seconds, that is, a minimal score of 1.[3,25,27]

EF composite score. We averaged the standardized (z) scores on the three tasks to achieve equal weighting and computed an EF composite score for each participant.

Statistical Analysis
Our main interest was the impact of prematurity on EF; hence, group comparisons in terms of GA were the main scope, that is, GA < 32 weeks (very preterm) versus GA ≥ 32 weeks (moderately preterm). In addition, sex and maternal education may modulate the preschool EF scores. Accordingly, scores on each of the EF tasks and proportion of successful task completion were analyzed with a Mann–Whitney U test and Chi-square test, respectively, or with the between-subject factors GA birth group, sex, and maternal education. To further investigate dimensional associations between EF and broader neurodevelopment, we also calculated Spearman correlations among GA, EF measures, BSID-III scores, and ASD risk . Correlations were interpreted in line with Cohen's recommendations, that is, correlation coefficients <0.30 were considered as little or no correlation, 0.30–0.50 low, 0.50–0.70 moderate, 0.70–0.90 high, and >0.90 very high.[28] Data were analyzed using SPSS.[26]

Results

Participant Characterization

From the 104 children that attended the 2-year follow-up, 97 completed the EF battery and 7 refused to cooperate due to fatigue infant and maternal characteristics, shown in ►Table 1. Sixty-five percent of infants in our sample were born before 32 weeks GA (16% before 28 weeks GA). The majority of preterm infants were boys (65%). Sixty-nine percent of the mothers reached a high maternal educational level. The mean corrected age at which the children were tested was 24.29 months (SD = 0.84).

The mean index score on BSID-III was 102 (SD = 20) for cognition, 92 (SD = 23) for language, and 106 (SD = 16) for motor function. Clinically identified ASD risk was present in 18% of the children and was clearly overrepresented in the younger GA group ($p = 0.006$).

Executive Function

An overview of group comparisons for the results on the EF measures is presented in ►Table 2. Most children were able to successfully complete the MSML (87%) and the SDT (67%), but only 22% of children successfully passed the RevCat.

MSML total score ($p = 0.025$) and MSML success rate ($p = 0.026$) were significantly higher in moderately preterm children as compared with the group of extreme and very preterm children. RevCat total score and RevCat success rate did not differ significantly between GA groups. Likewise, SDT total score did not differ between GA groups, but SDT success rate showed a trend to be higher in the moderately preterm infants ($p = 0.056$). No significant difference was found in the mean EF composite score between GA groups. There were no significant sex differences in any of the EF measures or in the EF composite measure. Pertaining to maternal educational level, a lower level of maternal education was significantly associated with a lower MSML total score ($p = 0.001$) and lower MSML success rate ($p = 0.001$). There was no significant impact of maternal educational level on performance on RevCat, SDT, or on the EF composite score.

Associations among Executive Function Abilities, General Development, and Autism Spectrum Disorder Suspicion

►Table 3 shows correlations between GA, the different EF measures, general developmental indices, and clinically identified ASD risk. Total scores for MSML, RevCat, and SDT were positively but rather weakly correlated with each other ($p < 0.01$). All BSID developmental indices were moderately correlated with each other ($p < 0.001$). A higher GA was associated with better scores on MSML and a lower ASD risk. All EF measures showed significant positive correlations with BSID-III cognition ($p < 0.01$) and BSID-III motor abilities ($p < 0.01$). The MSML total score was weakly but significantly correlated with the BSID language index ($p < 0.05$). A lower score on each of the EF and BSID measures was related to an increased risk on clinical evidence for ASD symptomatology ($p < 0.01$).

Table 2 EF group comparisons in terms of gestational age, sex, and maternal education. Data presented as mean (SD) or n (%)

	Full sample	Gestational age			Sex			Maternal education		
		<32 w (n = 63)	≥32 w (n = 34)	p-Value [a]	Male (n = 63)	Female (n = 34)	p-Value [a]	Low (n = 30)	High (n = 67)	p-Value [a]
Multisearch multilocation										
Total score, mean (SD)	8.19 (2.43)	7.78 (2.93)	8.94 (0.34)	**0.025**	8.08 (2.57)	8.38 (2.16)	0.721	7.20 (3.46)	8.63 (1.63)	**0.001**
Success, n (%)	84 (87)	51 (81)	33 (97)	**0.026**	54 (86)	30 (88)	0.728	21 (70)	63 (94)	**0.001**
Reverse categorization										
Total score, mean (SD)	0.98 (1.10)	1.00 (1.15)	0.94 (1.01)	0.923	0.92 (1.13)	1.09 (1.06)	0.267	0.87 (1.52)	1.03 (1.03)	0.138
Success, n (%)	21 (22)	15 (24)	6 (17.6)	0.482	13 (21)	8 (24)	0.741	7 (23)	14 (20.9)	0.788
Snack delay task										
Total score, mean (SD)	1.78 (1.28)	1.70 (1.30)	1.94 (1.25)	0.336	1.65 (1.32)	2.03 (1.19)	0.183	1.57 (1.41)	1.88 (1.23)	0.291
Success, n (%)	65 (67)	38 (60)	27 (79)	0.056	39 (62)	26 (77)	0.145	17 (57)	48 (71.6)	0.147
EF composite score, mean (SD)	0.00 (1.00)	−0.10 (1.11)	0.18 (0.73)	0.643	−0.09 (1.02)	0.17 (0.96)	0.164	−0.31 (1.28)	0.14 (0.82)	0.071

Abbreviation: EF, executive function.

[a] p-Values for group comparisons based on chi-square test or Mann–Whitney U test, p-values < 0.05 are presented in bold.

Table 3 Spearman correlations between GA, EF measures, and neurodevelopmental outcome at 2 years corrected age

	Gestational age	MSML total score	RevCat total score	SDT total score	EF composite score	BSID-III cognition	BSID-III language	BSID-III motor	ASD rating
Gestational age	1	0.238[a]	−0.036	0.096	0.047	0.082	0.098	0.177[a]	−0.322[b]
MSML total score		1	0.270[b]	0.336[b]	0.464[b]	0.411[b]	0.280[a]	0.345[b]	−0.472[b]
RevCat total score			1	0.320[b]	0.837[b]	0.417[b]	0.018	0.308[b]	−0.214[b]
SDT total score				1	0.729[b]	0.392[b]	0.217	0.289[b]	−0.399[b]
EF composite score					1	0.529[b]	0.116	0.401[b]	−0.345[b]
BSID-III cognition						1	0.640[b]	0.489[b]	−0.419[b]
BSID-III language							1	0.351[b]	−0.432[b]
BSID-Motor								1	−0.402[b]
ASD rating									1

Abbreviations: ASD, Autism spectrum disorder (high risk =1; low risk = 0); BSID-III, Bayley scales of infant and toddler development III; EF, executive function; MSML, Multisearch Multilocation Task; RevCat, Reversed Categorization Task; SDT, Snack Delay Task.
Note: Significance levels for Spearman's correlations: [a]$p < 0.05$; [b]$p < 0.01$.

Discussion

In this study, we investigated EF in preterm children and its relationship with GA, sex, maternal education, and neurodevelopmental outcomes at 2 years corrected age. EF has been established as a key predictor of future mental health and academic achievement. The earlier we can identify children at-risk because of low EF scores, the sooner intervention can start, resulting in the better future prognosis. However, most existing EF batteries have been developed for children over 4 years of age,[2] thereby limiting the possibilities of early detection. In the present study, we administered an adapted EF battery in a sample of 2-year-old prematurely born children and showed that it is a feasible instrument to measure individual differences in EF abilities at this age in children born preterm. The majority of children performed well on MSML and SDT, but a large part failed on RevCat. These observations align very well with the findings of Carlson,[23] who observed a similar performance level and order of EF task difficulty in 2-year-old term-born children. Thus, even though no normative data exist and no term-born population was included in our study, integration of the findings across both studies suggests a fairly similar developmental trajectory of EF abilities in preterm and term-born children, with cognitive flexibility generally taking longer to fully emerge.

In line with a recent review,[29] we found no significant sex differences in EF. Importantly, however, lower GA and maternal education were significantly associated with lower EF, in particular on the MSML task. Lower EF scores were associated with poor cognition and motor scores on BSID-III and with an increased risk on ASD. As this was based on a provisional clinical judgment, no firm conclusions can be made. Taken together, these findings point in the direction of EF as a potential early marker of altered behavior and development in prematurely born children. This is in line with other studies pointing toward the association between EF deficits and ASD,[23,25,30] including studies demonstrating

that EF was found to be highly associated with theory of mind, already from the age of 2 years.

The scores on the MSML, RevCat, and SDT subtests were weakly correlated, suggesting that they measure separate but related aspects of EF.[3] Based on task content and expert literature, we can assume that MSML is mainly related to spatial working memory, RevCat to cognitive flexibility, and SDT to inhibitory control. Since success rates for MSML and SDT were high, it seems feasible to measure inhibitory control and working memory at this age. In contrast, RevCat had a low success rate suggesting that cognitive flexibility tasks are challenging at this age. This confirms previous data showing that cognitive flexibility is a complex, later-developing ability (between age 3–4 years) that is made possible by improvements in inhibitory control and working memory.[5,23,31] However, interpretation of the scores is challenging as no normative data are available for term-born children, which is a major limitation of the present study.

Children born before 32 weeks GA were more likely to fail MSML, implying that their spatial working memory is not developed as well as in children born moderately preterm. Previous findings suggest that very preterm children with spatial working memory difficulties demonstrate evidence of less neural efficiency in frontal brain areas.[32] However, with increasing age and performance, compensational mechanisms seem to occur.[32] In this regard, the exact EF developmental trajectories throughout childhood remain unclear, that is, whether preterm infants continue performing poorer in EF than their peers, or whether they catch up in performance with increasing age.[33]

Unexpectedly, GA was not an independent predictor of individual differences in inhibitory control and cognitive flexibility. While GA has been shown to have a clear association with survival rates and severe neurodevelopmental delays of preterm infants, possibly there is more variability in how GA impacts higher-order cognitive processes.[34] Indeed, in addition to lower GA, studies have shown that other biological factors such as BW, Apgar score,

and neonatal complications are also related to EF in preterm children.[4,35]

A higher maternal educational level was associated with a significantly higher MSML total score and success rate. In addition to possibly genetically transmitted influences, the family investment model is a known theoretical model to explain the relationship between education and EF. This model posits that low-educated parents have fewer resources to provide children with cognitively stimulating learning materials and experiences which are critical for neurocognitive development.[36] Therefore, early counseling of low-educated parents may improve outcomes.[36]

Studying the outcome of preterm infants remains critical to enable early identification of high-risk children and to provide appropriate support.[2,17,37] BSID-III is a widely used measure to study neurodevelopmental outcomes in preterm infants.[20] In contrast to other studies, BSID-III scores in our cohort were comparable with scores in term-born children.[37,38] These results might be explained by the fact that we not only included children born extremely preterm and because of the exclusion of children with severe brain lesions in our cohort. EF results correlated moderately with BSID-III scores. We, therefore, suspect that EF highlights a different dimension of neurodevelopment compared with BSID-III. Based on recent research demonstrating that EF is a better predictor of behavioral and academic outcomes than intelligence quotient and motor functioning,[2] we propose that EF testing can be of added value in preterm infants. Long-term follow-up is necessary to test this hypothesis.

Findings consistently report that poorer EF co-occurs with internalizing and externalizing behavior.[39] Poorer EF is also characteristic of ADHD and ASD, which are more prevalent in preterm infants than in term-born peers.[2] In line with the current literature, we found lower EF scores and higher failure rates in children with clinically identified ASD risk, confirming the association between EF difficulties and the vulnerability to develop neurodevelopmental problems.

Conclusion

This study provides evidence that the administered EF battery is valuable to assess EF in 2-year-olds born preterm. Lower gestational age and maternal education are related to poorer EF, in particular spatial working memory, and better executive function in this young cohort is associated with better outcomes. Executive functions can therefore be a valuable target for early intervention, resulting in improvements in neurodevelopmental outcomes in children born preterm.

What this Paper Adds

- Executive function can be assessed in 2-year-olds born preterm.
- Preterms performed well on inhibition and working memory but failed cognitive flexibility.
- Executive function is associated with gestational age and maternal education but not with sex.

- Executive function is positively correlated with cognition and motor function.
- Autism risk was associated with low executive function scores.

Clinical Trial Registration
Full name AND URL of the registry: ClinicalTrials.gov (http://www.clinicaltrials.gov/)
Registration number of your study: NCT02623400
Type of study: Prospective

Conflict of Interest
None declared.

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