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Early life stress, kangaroo care, parenting behavior and secure attachment predict executive functioning in 2 year olds born preterm

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Self-regulation and executive functioning are known key predictors of future cognitive development and mental health. We examined the effect of early life neonatal stress, maternal perinatal stress, kangaroo care, maternal parenting behavior and secure child attachment on executive function at 2 years corrected age (CA) in children born preterm (i.e. < 34 weeks of gestation and/or <1500 g birth weight). Neonatal child characteristics were recorded at the Neonatal Intensive Care Unit (NICU). We examined self-reported perinatal maternal stress during NICU stay, maternal emotional availability at 4 months CA, and child attachment security at 14 months CA. The executive function battery at 2 years CA was completed by 97 children. Low birth weight, a high number of skin breaking procedures and high level of maternal stress predicted lower executive function scores. Kangaroo care, non-intrusive maternal parenting behavior and secure attachment were associated with higher executive function scores. Even after controlling for background factors, modifiable factors such as neonatal child and mother stress, kangaroo care, parenting style, and child attachment style uniquely predict later executive functioning development, indicating that preventive interventions need to integrate multiple aspects of neuroprotective care, including supporting the child-parent bond, both at the NICU and beyond.

Keywords Preterm, Executive function, Early life stress, Kangaroo care, Attachment, Parenting

Children born preterm and hospitalized in the neonatal intensive care unit (NICU) are exposed to significant early life neonatal stress such as mechanical ventilation, painful medical procedures and maternal separation[1]. Early stress exposure may alter biological processes, such as the immune system, the autonomic nervous system, the hypothalamic-pituitary-adrenal axis, as well as gene expression. These alterations may subsequently affect brain development and contribute to neurodevelopmental impairments in children born preterm, a process referred to as biological embedding of neonatal stress exposure[2]. Studies have shown that increased exposure to stressors in the NICU is associated with decreased size of frontal and parietal brain regions, altered structural and functional connectivity within the temporal lobes, and slower development of autonomous arousal regulation[3–7]. As executive function skills are primarily hosted in the prefrontal cortex, a neural structure characterized by its late and prolonged maturation pattern, we also expect an influence of early life neonatal stress on executive functioning in children born preterm[8].

It is well known that neonatal risk factors, such as gestational age and birth weight, are negatively associated with executive function[9,10]. Maternal educational level is also an important predictor of (preterm) infant's cognitive development, regardless of gestational age[11–13]. Evidence suggests that the impact of early life stress on

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preterm infants' neurodevelopment also depends on other aspects of the parental environment. In particular, the positive effect of parental presence and involvement in the NICU, and especially of kangaroo care, is well-studied in preterm children. Kangaroo care, also known as skin-to-skin contact, may reduce the effect of early life stress on brain development, as it accelerates the autonomic and neurobehavioral maturation in preterm infants[14–16]. Also, sensitive parenting and responsive interactions between mother and child are protective factors, not only because of their impact on social motivation and bonding, but also because of their positive impact on the development of prefrontal brain systems[17]. Note, however, that these generally protective parental mechanisms are at risk in families of preterm infants. Indeed, parents may perceive the preterm birth and NICU hospitalization as traumatizing, thereby eventually disrupting the parents' ability to provide sensitive support and scaffolding for their child[18].

Thus far, previous studies have investigated these potential risk and protective factors for EF in a rather isolated or fragmentary manner, often examining only single elements such as the number of painful procedures or the effects of kangaroo care. Here, in contrast, we aim to provide a comprehensive and overarching understanding of the dynamic interplay among several of the key factors that determine the development of executive functioning in a vulnerable prematurely born population. We hypothesize that executive function development in children born preterm is not only impacted by classical neonatal risk factors and maternal education, but that also other factors like parental stress, responsivity and infant bonding may exert unique negative or protective influences.

Methods

Participants

This study describes a cohort of children from the Resilience study, a prospective single-center cohort study with longitudinal follow-up, which was registered at Clinical Trials.gov (NCT02623400). The study was approved by the Ethical Committee of the University Hospital Leuven and is performed in accordance with the Guidelines for Good Clinical Practice (ICH/GCP) and the latest version of the Declaration of Helsinki.

Children born at University Hospitals Leuven between August 2016 and July 2018 were recruited if they were born before 34 weeks gestational age and/or had a birth weight lower than 1500 g. Informed consent was obtained from parents within the first week after birth, after being informed about the study. Exclusion criteria were the following: (a) maternal age less than 18 years, (b) the inability of a parent to speak and understand Dutch or English, (c) unstable medical (somatic and/or psychiatric) disease in the parent(s) and (d) the presence of a major congenital malformation or major central nervous system pathology (grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia detected on cranial ultrasonography during the neonatal phase) in the preterm infant.

Procedure

Preterm infants were followed from birth to 2 years CA at different time points: birth, 4 months, 14 months, and 2 years CA. Assessments, including Bayley III psychomotor (PDI) and mental developmental (MDI) evaluation, were conducted by a certified physiotherapist, psychologist, and a physician.

Measures

Child and maternal characteristics

Birth characteristics of the infant, such as sex, gestational age, birth weight and Apgar scores, were retrieved from the child's record. As a reflection of socioeconomic status and maternal cognitive ability, maternal education was assessed according to the ISCED scale of the UNESCO Institute for Statistics[19] by converting classifications on the original 7-point scale to a 2-point scale (low/high) with 'low education' corresponding to mothers that obtained a secondary school degree or less, and 'high education' corresponding to mothers who obtained at least a bachelor degree. Dichotomizing the response categories resulted in a pronounced bimodal distribution.

Early life neonatal stress

Early life neonatal stress was defined as the cumulative number of skin-breaking procedures experienced up till 5 days after birth. These data were retrieved from the electronic patient data sheet. The number of skin-breaking procedures was calculated comprising events such as heel lance, intramuscular injection, chest tube insertion, and central line insertion, as previously described for this cohort[5].

Maternal NICU stress

Mothers were asked to complete the NICU Parental Stressor Scale (PSS-NICU), both at the end of the first postnatal week and at their infants' discharge to home. The PSS-NICU is designed to measure parental perception of stressors arising from the physical and psychosocial environment of the NICU. It contains 26 items that measure stress related to (a) sights and sounds, (b) appearance and behavior of the infant, (c) the impact on parent's role and their relationship with their baby, and (d) the parents' relationship and communication with the staff. The responses are scored on a 5-point Likert scale. An average total score was calculated based on all items, with higher scores indicating more experienced stress[20].

Kangaroo care

Mean daily amount of maternal kangaroo care (KC), defined as the total minutes of KC by the mother divided by the number of hospitalization days, was recorded. Both nursing staff and parents marked the start and stop time of kangaroo care rigorously. The parent and staff files were matched and the total duration of kangaroo mother care per day was calculated.

Maternal parenting behavior

The Emotional Availability Scales (EAS), developed by Biringen, Robinson & Emde[21], were used to measure the quality of mother-child interaction at 4 months CA during a 10-minute free play session that was video recorded. Mothers were provided with a bag of various toys and instructed to play with their baby on a play mat as they would do at home. EAS rates six dimensions of the emotional availability of the mother towards the child, and of the child towards the mother. The score of each dimension ranges from 0 to 29 and the higher the score, the better. The four adult dimensions are sensitivity, structuring, non-intrusiveness, and non-hostility, whereas the two child dimensions are the child's responsiveness to the parent and the child's involvement of the parent. For this study, we focused on the adult dimensions of the EAS to evaluate the quality of mother-infant interaction. Sensitivity refers to the adult's ability to be warm and emotionally connected with the child, and involves qualities such as responsiveness to the child, accurate reading of the child's communications, and ability to smoothly resolve conflicts. The structuring scale assesses the degree to which the adult appropriately structures the child's play, for instance, by taking care to follow the child's lead and by setting limits for appropriate child behavior and/or misbehavior. Non-intrusiveness refers to the ability to be available to the child without being intrusive to him/her, with intrusiveness implying overdirectiveness, overstimulation, interference, or overprotectiveness. The adult non-hostility scale assesses the degree of (non)hostility, ranging from no observed hostility over covert to overt forms. The EAS was scored by two certified coders who were blinded from any background information about the baby and mother. Both coders were trained by Biringen to achieve interrater reliability ($r > 0.80$) with Biringen[21]. The first 10 cases were independently coded by both raters. Intraclass correlation coefficients for each scale were as follows: sensitivity (ICC = 0.97, $p < 0.001$), structuring (ICC = 0.92., $p < 0.001$), nonintrusiveness (ICC = 0.88, $p < 0.001$), and nonhostility (ICC = 0.83, $p < 0.001$). The coders then reviewed these cases together and discussed their ratings to reach consensus.

Child attachment security

To measure mother-child attachment, we conducted the strange situation procedure (SSP), developed by Mary Ainsworth, at 14 months CA. The SSP, by prompting attachment behavior in the child, allows for standardized classification of attachment security[22]. It consists of 8 episodes. In episode 1–3, the child is first confronted with a strange environment and then with a stranger. During the 4th episode, the mother leaves the room, and the infant is left with the stranger. The mother returns during the 5th episode and the stranger leaves. The mother then leaves again in episode 6, which means the infant is alone in the room. The stranger returns in episode 7, and eventually the mother also returns in episode 8. The strange environment, the stranger and the separations from the mother make it stressful for children and prompt attachment behavior. During episode 5–8, it is evaluated how much the child trusts the mother by looking at the child's behavior and how long it takes before the balance between exploration of the environment and focus on the mother has again been restored. The way in which the child approaches the mother at the reunion and seeks contact or tries to avoid contact, is angry, or acts in a disorganized way, is decisive for the attachment classification. Children's attachment to their mother can be classified as secure (B), insecure avoidant (A), insecure ambivalent (C), or disorganized (D). Based on this classification system, we have opted for a binary score: secure attachment (B) versus insecure attachment (A-C-D). Based on video recordings, the SSP was coded by a single independent certified coder (reliable with A. Sroufe) that was blind to any background information.

Executive function

Research has shown that preterm infants are particularly impaired in three core executive functions, i.e. working memory, cognitive flexibility and response inhibition[10]. Accordingly, executive function was assessed at 2 years CA using three age-appropriate tasks as described earlier in this cohort[23] and illustrated in Fig. 1. The Multisearch Multilocation Task mainly taps into spatial working memory, the Reversed Categorization Task in cognitive flexibility, and the Snack Delay Task in inhibitory control[11,24–26]. Detailed information about the procedure and scoring has been described earlier[23]. In line with this study, a summary executive function (EF) composite score was determined by averaging the standardized (z) score on each of the three tasks, thereby giving equal weight to working memory, flexibility and inhibition.

Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 26.0[27]. Missing data were dealt with using an expectation maximization algorithm, as data were missing at random according to Little's MCAR test. First, we calculated Pearson correlations (as data were normally distributed) to examine bivariate associations among all the measures. Next, to examine the unique and independent contribution of each of the variables towards predicting individual differences in executive function, a five-step hierarchical regression analysis was conducted, retaining only the variables that significantly correlated with executive function. Prior to this regression analysis, the assumption of multicollinearity was verified.

The major aim of this hierarchical regression analysis is to examine the independent contributions of fixed prematurity measures (birth weight and Apgar score) and background variables (maternal education), as well as the extent to which potentially modifiable risk and protective factors (early life neonatal stress, maternal NICU stress, kangaroo care, maternal parenting behavior and attachment security) can predict executive function above and beyond these fixed prematurity measures. Accordingly, prematurity indices (birth weight and Apgar score) were entered in stage 1, and maternal education was entered in stage 2. Next, a series of potentially modifiable risk and protective factors were entered: The number of experienced skin-breaking procedures, as an index of early life neonatal stress, in stage 3; maternal stress experienced at NICU in stage 4; and potentially protective measures such as kangaroo care, non-intrusive maternal parenting behavior and attachment security in stage 5. To estimate the unique contribution of each of these measures, standardized beta coefficients and

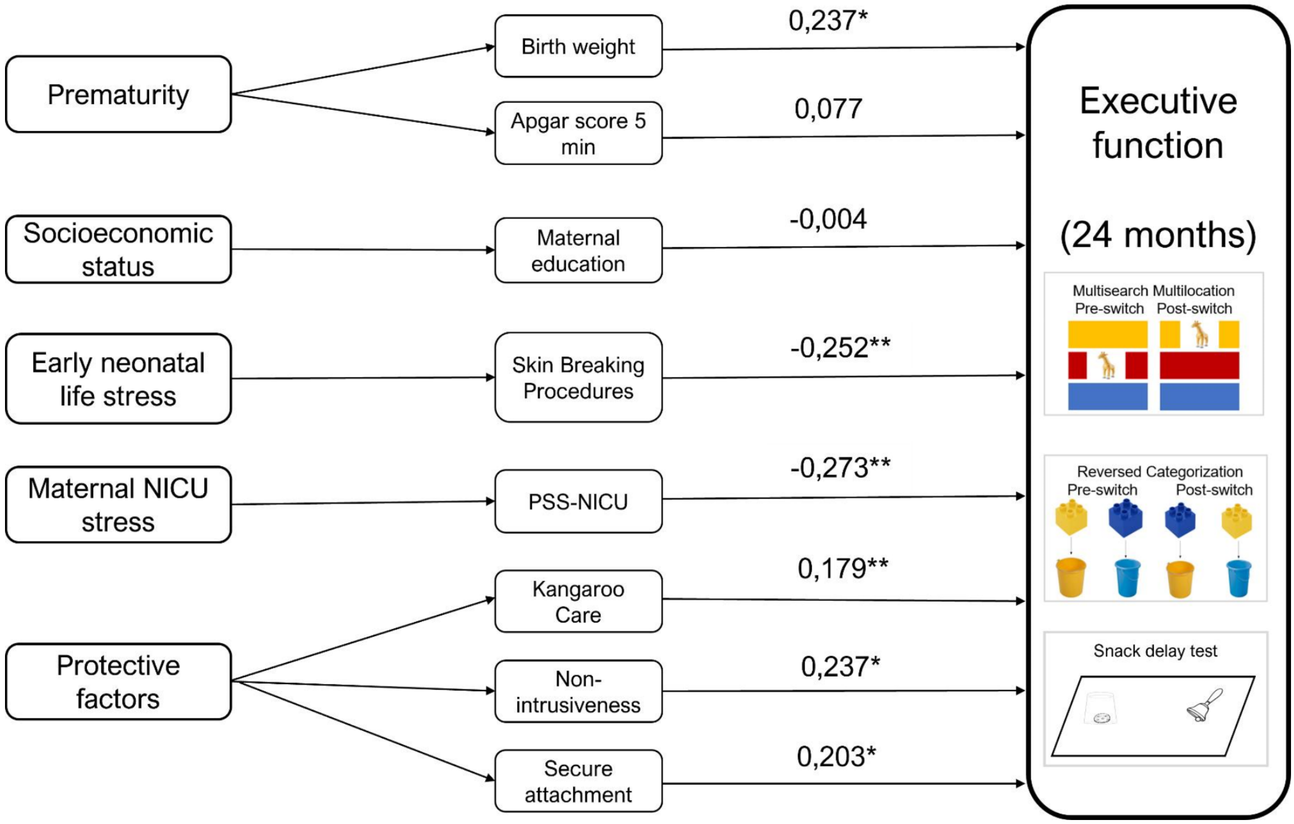

Fig. 1. Visual representation of the full hierarchical multiple regression model predicting executive function at 2 years of age in preterm infants ($n = 97$) from variables related to prematurity and early life stress, as well as socio-economic status, maternal risk and protective factors. The numbers next to each arrow indicate standardized Beta coefficients with corresponding significance levels (* $p < 0.05$, ** $p < 0.01$). PSS-NICU: parental stressor scale neonatal intensive care unit.

respective p-values are calculated. Model improvement is evaluated by R^2 change and respective p-values. Statistical significance was defined as $p < 0.05$. Data in the text are means and standard deviations (SD) or N (%).

Results

Patient sample

From the original group of 144 preterm children that took part in the Resilience study at NICU, 118 returned for the neuropsychological assessment at 2 years CA and 97 children completed the executive function battery. Missing assessments were mainly due to COVID-19 testing complications and because some children refused to cooperate due to fatigue. Characteristics of the patient sample are shown in Table 1. The mean scores of 106.3 (15.59) on the Bayley-III PDI and 102.29 (20.09) on the Bayley III-MDI indicate that, in general, toddlers in our cohort show a normal cognitive and motor function at the age of 2 years.

Bivariate associations among the measures: correlation matrix

Bivariate correlations for all the included measures are shown in Table 2. As expected, birth weight and gestational age were highly correlated ($r = 0.768$, $p < 0.01$). Both parameters also correlated with the Apgar score (GA: $r = 0.337$, $p < 0.001$; BW: $r = 0.269$ $p = 0.008$) and with the number of skin-breaking procedures (GA: $r = -0.361$, $p < 0.01$; BW: $r = -0.175$, $p = 0.087$). There was no significant correlation between these baseline neonatal variables and maternal stress at NICU, the amount of maternal kangaroo care, maternal parenting behavior or child attachment security. Yet, birth weight ($r = 0.293$, $p = 0.004$) and Apgar scores ($r = 0.225$, $p = 0.026$) correlated positively with executive function at 2 years CA. Also, maternal education ($r = 0.207$, $p = 0.042$), the amount of kangaroo care ($r = 0.300$, $p = 0.003$), non-intrusive parenting behavior ($r = 0.245$, $p = 0.016$) and secure attachment ($r = 0.238$, $p = 0.024$) were positively related to EF at 2 years. Infant stress (skin breaking procedures ($r = -0.373$, $p < 0.001$)) and maternal stress ($r = -0.259$, $p = 0.010$) were negatively related to EF at 2 years CA.

Unique neonatal stress and bonding predictors for executive function

To study the role of possible predictive neonatal and maternal factors for executive function, we conducted a five-step hierarchical regression model with executive function as the dependent variable (Table 3). Neonatal risk factors (birth weight and Apgar score) were entered at stage one of the regression to control for these non-modifiable neonatal risk factors.

Patient characteristics	Preterm $N = 97$
Maternal education (%)	69% high, 31% low
Gender (%)	65% male, 35% female
Gestational age at birth (weeks)	30.16 ± 2.41 (23.6–33.6)
Birth weight (grams)	1395.81 ± 401.19 (576–2300)
Apgar score 5 min after birth	7.74 ± 1.60 (2–10)
Experienced infant stress: Skin-breaking procedures day 5 (number)	41.06 ± 26.92 (6-136)
Experienced maternal stress: Parental stressor scale	2.58 ± 3.29 (1–33)
Maternal skin-to-skin contact: average daily minutes of Kangaroo care	76.63 ± 38.82 (8-291)
Maternal Emotional Availability	
EAS sensitivity	24.48 ± 3.43 (11–29)
EAS structuring	24.40 ± 3.33 (13–29)
EAS non-intrusiveness	21.26 ± 4.20 (13–29)
EAS non-hostility	25.60 ± 2.14 (20–30)
Secure attachment (%)	64% secure, 36% insecure
Bayley-III Mental developmental index	102.29 ± 20.09 (60–135)
Bayley-III Psychomotor developmental index	106.30 ± 15.59 (53–139)
Multisearch multilocation, total score	8.19 ± 2.34 (0–9)
Reverse categorization, total score	0.98 ± 1.10 (0–3)
Snack delay test, total score	1.78 ± 1.28 (0–3)
EF composite score	0 ± 0.73 (− 1.89–1.04)

Table 1. Patient characteristics. Data presented are mean ± SD (range) or N, %. *EAS* emotional availability scale, *EF* executive function.

The hierarchical multiple regression revealed that birth weight contributed significantly to the regression model (ß = 0.269, $p = 0.013$) and together with Apgar evaluation accounted for 10.7% of the variation in executive function at 2 years CA ($p = 0.007$). Introducing maternal education, explained an additional non-significant 3.1% of variation in executive function (p-value R^2 change = 0.082). Adding early life infant stress (skin-breaking procedures: ß = − 0.279, $p = 0.005$) to the regression model explained an additional 7.7% of the variation in executive function and this change in R^2 was significant (p-value R^2 change = 0.005). Likewise, adding maternal stress (PSS-NICU: ß = − 0.244, $p = 0.011$) to the regression model, explained an additional significant 5.8% of the variation in executive function (p-value $R<^2$ change = 0.011). Finally, when we add a series of protective factors such as kangaroo care (ß = 0.245, $p = 0.007$), non-intrusive maternal parenting behavior (ß = 0.179, $p = 0.048$) and secure attachment (ß = 0.203, $p = 0.031$) to the regression model, each of them uniquely and significantly contributed to explaining EF variability, and together they explained an additional 15.0% of variation in executive function (p-value R^2 change < 0.001). When all independent variables were included in stage five of the regression model, neither Apgar scores nor maternal education were significant predictors of executive function, but all other variables uniquely contributed. Together this set of fairly remote neonatal and socio-affective variables accounted for 42.3% of the variance in executive function at 24 months CA. The results of the full regression model are summarized in Fig. 1.

Discussion

One of the first and most important challenges of the newborn child, and especially the prematurely born neonate, is learning to regulate their autonomic functions, such as sleep-wake cycles, breathing, heart rate, arousal regulation, feeding cycles, etc[28]. Initially supported by parental co-regulation, the child gradually masters self-regulation of these autonomic functions, subsequently also resulting in more advanced emotional and cognitive regulation, including more developed executive functioning abilities[29,30]. In this study, we followed a cohort of prematurely born children and investigated to what extent indices of prematurity and early life neonatal child and maternal stress are associated with altered executive function at 2 years CA, and whether a protective environment can buffer these effects. We confirmed that prematurity and exposure to early life neonatal and maternal stress are critical determinants of executive function development, since low birth weight, high levels of infant skin-breaking procedures and high levels of maternal NICU stress uniquely predicted lower executive function scores two years later. Conversely, more skin-to-skin care at the NICU, a non-intrusive maternal parenting style during the early months of life, and the presence of a secure attachment constellation in toddlerhood are protective factors, as they were all uniquely associated with higher executive function scores.

Preterm infants are usually classified in terms of gestational age and birth weight. While both characteristics were highly correlated in our study, rather unexpectedly, only birth weight was significantly associated with executive function. While gestational age has been shown to have a clear association with motor function in preterm infants[31], studies have shown that other biological factors such as birth weight, Apgar score and neonatal complications are more strongly related to executive function in these children, this in addition to lower gestational age[12]. Indeed, previous literature pointed out that lower birth weight is associated with lower

	Maternal education	Gender	GA	BW	Apgar	SBP	PSS-NICU Day 5	PSS-NICU discharge	KC	Sensitivity	Structuring	Non-intrusiveness	Non-hostility	Secure attachment	EF
Maternal education	1	− 0.116 (0.257)	0.040 (0.694)	− 0.037 (0.716)	0.207* (0.042)	− 0.280 ** (0.005)	− 0.060 (0.561)	0.075 (0.464)	0.097 (0.346)	0.060 (0.559)	0.033 (0.749)	0.166 (0.104)	0.129 (0.206)	0.353** (< 0.001)	0.207* (0.042)
Gender		1	0.036 (0.726)	− 0.12 (0.910)	0.152 (0.136)	0.025 (0.807)	− 0.033 (0.747)	− 0.140 (0.171)	− 0.165 (0.107)	0.070 (0.498)	0.067 (0.515)	− 0.158 (0.122)	− 0.113 (0.269)	0.018 (0.864)	0.124 (0.225)
Gestational age			1	0.768** (< 0.001)	0.337** (< 0.001)	− 0.361** (< 0.001)	− 0.323** (0.001)	− 0.080 (0.434)	−0.067 (0.517)	0.096 (0.350)	0.084 (0.411)	0.130 (0.205)	0.043 (0.679)	− 0.122 (0.253)	0.151 (0.139)
Birth weight				1	0.269** (0.008)	− 0.175 (0.087)	− 0.311** (0.002)	− 0.071 (0.491)	− 0.077 (0.455)	− 0.018 (0.860)	− 0.037 (0.721)	0.158 (0.122)	0.011 (0.914)	− 0.130 (0.223)	0.293** (0.004)
Apgar					1	− 0.079 (0.444)	− 0.019 (0.856)	− 0.061 (0.555)	0.055 (0.592)	− 0.093 (0.365)	− 0.101 (0.325)	0.050 (0.626)	− 0.071 (0.491)	0.023 (0.833)	0.225* (0.026)
Skin breaking procedures						1	− 0.204* (0.045)	0.060 (0.559)	− 0.169 (0.098)	− 0.111 (0.278)	− 0.078 (0.445)	0.077 (0.451)	− 0.303** (0.003)	− 0.114 (0.283)	− 0.373** (< 0.001)
PSS-NICU Day 5							1	0.154 (0.131)	0.070 (0.499)	0.012 (0.904)	− 0.058 (0.570)	− 0.111 (0.280)	0.084 (0.411)	0.092 (0.390)	− 0.088 (0.391)
PSS-NICU discharge								1	0.059 (0.564)	0.046 (0.653)	0.069 (0.504)	0.011 (0.913)	0.055 (0.593)	0.089 (0.406)	− 0.259* (0.010)
Kangaroo care									1	0.070 (0.495)	0.069 (0.504)	0.067 (0.514)	0.123 (0.229)	0.162 (0.127)	0.300** (0.003)
Sensitivity										1	0.781** (< 0.001)	0.366** (< 0.001)	0.636** (< 0.001)	0.018 (0.870)	0.072 (0.483)
Structuring											1	0.292** (0.004)	0.440** (< 0.001)	0.023 (0.830)	0.098 (0.340)
Non-intrusiveness												1	0.437** (< 0.001)	0.117 (0.271)	0.245* (0.016)
Non-hostility													1	0.054 (0.615)	0.080 (0.437)
Secure attachment														1	0.238* (0.024)
EF															1

Table 2. Pearson correlations between neonatal factors, parental factors and executive function. *GA* gestational age, *BW* birth weight, *SBP* skin-breaking procedures, *PSS-NICU* Parental stressor scale neonatal intensive care unit, *KC* kangaroo care, *EF* executive function. Pearson significance level: *$p < 0.05$, ** $p < 0.01$.

Step	Variables entered	ß coefficients	p-value	Model R^2	p-value R^2	R^2*Change*	p-value R^2*Change*
1	Birth weight Apgar 5 min	0.269 0.121	0.013 0.260	10.7	0.007		
2	Birth weight Apgar 5 min Maternal education	0.281 0.085 0.179	0.009 0.428 0.082	13.8	0.005	3.1	0.082
3	Birth weight Apgar 5 min Maternal education SBP	0.221 0.102 0.089 -0.297	0.035 0.327 0.389 0.005	21.5	< 0.001	7.7	0.005
4	Birth weight Apgar 5 min Maternal education SBP PSS-NICU	0.215 0.081 0.114 -0.274 -0.244	0.034 0.421 0.255 0.007 0.011	27.3	< 0.001	5.8	0.011
5	Birth weight Apgar 5 min Maternal education SBP PSS-NICU Kangaroo care Non-intrusiveness Secure attachment	0.237 0.077 -0.004 -0.252 -0.273 0.245 0.179 0.203	0.015 0.402 0.970 0.008 0.002 0.007 0.048 0.031	42.3	< 0.001	15.0	< 0.001

Table 3. Hierarchical regression analysis predicting executive function in 2-year-olds born preterm: model summary. *SBP* Skin-breaking procedures, *PSS-NICU* Parental stressor scale neonatal intensive care unit.

inhibitory control and lower achievement on visuospatial skills in extremely preterm children, which could both affect later academic performance[32].

Studies have shown that executive functioning is highly heritable, and that maternal intelligence and maternal EF predict intelligence and EF in the offspring[33]. In a similar way, studies have shown that parental socioeconomic status predicts executive function in the offspring[34]. In the present study, maternal education was assessed, which may reflect both maternal cognitive abilities (including maternal EF) and socioeconomic status. In addition to genetic factors, the relationship between low maternal education and lower executive function in the offspring has been explained by the family investment model[35]. This model posits that parental education, job status and the family's economic resources contribute to parental investment, which in turn affects children's cognitive, behavioral and health outcome. Children of low-educated parents might therefore have less access to cognitively stimulating learning materials and experiences, which are critical for neurocognitive development[36]. Our bivariate association matrix indeed showed a positive and significant correlation between maternal education and child executive function. Yet, the hierarchical regression model revealed no unique contribution of maternal education predicting executive function after controlling for basic neonatal factors, possibly due to the association of maternal education and the Apgar score.

As mentioned, Grunau et al. (2009) showed that preterm infants with greater early life neonatal stress exposure, expressed as the number of experienced skin-breaking procedures, have poorer motor and cognitive functioning at 8 and 18 months CA than those undergoing fewer skin-breaking procedures[37]. Our data enrich these findings by showing that preterm infants experiencing higher amounts of skin-breaking procedures also show lower executive function scores, even after correcting for any of the other variables. As complex, higher-order cognitive skills such as executive function are primarily located in the prefrontal cortex, a brain region that is in full development in the first months after birth, they may therefore be particularly vulnerable for the deleterious effects of early adverse experiences[38,39].

We also evaluated the impact of maternal NICU stress on executive function development in children born preterm. This assessment provides a global measure of self-reported stress mothers experienced during their child's NICU stay, including stress related to the physical appearance of the infant and the disruption of the anticipated parental role[20]. While we did not find studies that directly examined the relationship between early maternal NICU stress and infant outcome, there is evidence suggesting that high levels of maternal NICU stress may result in persistent maternal mental health issues, such as postpartum depression or post-traumatic stress disorder[40], which in turn have been shown to negatively impact long-term executive function development in the child[41,42]. Against this background, a more thorough and extensive early screening for maternal stress related to preterm birth may be critical to detect high risk maternal interactions at an early stage and provide timely psychological support.

We hypothesized that a protective environment may partially buffer the adverse effects of prematurity and early life neonatal and maternal stress. Several studies have shown that kangaroo care mitigates the effects of early life neonatal stress and promotes better cognitive, socio-affective and motor function in children born preterm[2,15,16]. The findings of this study demonstrate that maternal kangaroo care is also related to better executive function outcome, providing further evidence for the essential role of affective touch on infants' self-regulatory capacities, and ensuing socio-emotional and cognitive development[43]. Therefore, early and prolonged kangaroo mother care needs to be implemented by providing information about the benefits and feasibility of kangaroo care to medical staff and parents, as is highly recommended in the recently published WHO global position paper on this topic[44].

In addition, we examined the effect of maternal parenting behavior on executive function. Studies showed that greater sensitive parenting and caregiver-child mutuality, and less intrusive parenting predicts better child executive function[45]. We only included non-intrusive maternal parenting behavior in our hierarchical regression analysis since maternal sensitivity was not significantly correlated with executive function in our study. This finding is not unexpected as research showed that non-intrusive maternal parenting behavior is only weakly (negatively) correlated with maternal sensitivity, suggesting that -although the constructs are related- mothers may display aspects of both sensitivity and intrusiveness, although in varying amounts. Thus, it is valuable to consider non-intrusive maternal parenting behavior separately from other parenting constructs to understand how maternal behavior can support or interfere with development[17]. The observation that non-intrusive maternal parenting behavior was uniquely associated with higher executive function scores, may resonate with earlier findings showing that non-intrusive parental co-regulation promotes the emergence of self-regulatory abilities in the child, and thus also later executive functions[46,47].

Also, the quality of early attachment relationships with the primary caregivers emerged as a unique predictor of executive function in children, both in our study and in other studies[48–50]. Attachment security is defined as the quality and the representation of the enduring emotional bond forming during the first year of life between a child and his or her primary caregivers[51]. Secure parent-child attachment relationships provide a safe and harmonious environment in which children can experience successful dyadic regulation with their caregivers, especially when exposed to emotional or cognitive challenges[48,49,51]. Securely attached children use attachment figures as a secure base to explore from and return to. Insecurely attached infants either avoid their caregiver or fail to act independently in stressful situations[52]. Studies show that children who were more securely attached to their mothers in toddlerhood showed better performance on executive function tasks at 3 and 5 years of age[48]. It is believed that secure attachment relationships provide children with repeated experiences of successful dyadic regulation with the support of a competent caregiver. With time, securely attached children are expected to gradually internalize the regulatory strategies learned with the caregiver and eventually use them independently, such as during executive function tasks that require independent self-regulation. Hence, secure attachment relationships may provide children with emotional and cognitive skills supporting their developing self-regulatory capacities and thus their executive development[48,49,51]. We did confirm that children born preterm who are securely attached to their mothers had superior executive function scores, even as young as 2 years of age.

Therefore, our results further highlight that supporting the parent-child attachment relationship should be a cornerstone of early intervention programs for preterm infants[53]. Interestingly in this regard, both the *Newborn Individualized Developmental Care and Assessment Program* (NIDCAP) and the *Family Nurture Intervention* (FNI), two evidence-based NICU intervention programs focused on supporting the child-parent bond, report enhanced neural connectivity with frontal cortical brain areas[54,55], as well as improved executive functioning at school age in a group of moderately preterm children[56] and in a group of preterm infants with an intrauterine growth restriction[57]. The sensitive period just after NICU discharge - also characterized by significant autonomic, state, and motor regulation development—also presents an opportunity for intervention. Interestingly, post discharge responsive parenting programs for preterm infants and their families, such as the Infant Behavioral Assessment and Intervention Program (IBAIP) and the TOP Program in the Netherlands, have shown positive effects on both parenting behavior and behavioral regulation in preterm children (see[58] for a recent review on this topic).

We acknowledge that the relatively modest sample size of our study ($N = 97$), partially due to loss to follow-up during the COVID-19 pandemic, limits its generalizability to the broader preterm population. More research is needed to confirm our findings. Furthermore, while we only investigated maternal distress, skin-to-skin contact and behavior in this study, it is likely that also paternal emotional distress, skin-to-skin contact and parenting behavior may have a (compensatory) impact on the development of executive functions of a preterm infant. Yet, these paternal aspects have been hardly studied (but see[59] for a notable exception). Similarly, also in our study, fathers were less keen to complete questionnaires and were less systematically present during follow-up moments, limiting opportunities to observe their behavior and the attachment constellation with their infant.

It is interesting to note that Bayley-III MDI and PDI scores in our cohort of preterm toddlers are comparable with scores in full term children. We aimed to study a representative and fairly homogeneous group by including infants < 34 weeks GA, without severe brain pathology. Executive function scores correlated only moderately with Bayley-III scores, as described earlier in detail for this cohort[23]. Since recent research demonstrates that executive function is a better predictor of behavioral and academic outcomes than IQ and motor functioning[60], executive function is an interesting target in the search for early markers of (atypical) development. Future research with long-term follow-up is needed to support this.

Conclusion

Early life neonatal stress and maternal NICU stress are critical determinants of executive function development in 2-year-olds born preterm. Kangaroo care, non-intrusive maternal parenting behavior, and secure attachment are positively related with executive function development in these children. Our findings underscore the importance of early detection of infant and maternal NICU stress, intrusive parenting, and insecure attachment patterns. Implementing early interventions targeting these modifiable factors has the potential to significantly enhance executive function outcome.

Data availability
The data contains sensitive information that might lead to identification of infants or their parents. Parents did not provide consent for publicly sharing the data. The anonymized data are available upon reasonable request, query can be directed to Dr. Bieke Bollen or Prof. Gunnar Naulaurs.

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References
1. D'Agata, A. L. et al. Infant Medical Trauma in the neonatal Intensive Care Unit (IMTN): a proposed Concept for Science and Practice. *Adv. Neonatal Care*. **16** (4), 289–297 (2016).
2. Nist, M. D., Harrison, T. M. & Steward, D. K. The biological embedding of neonatal stress exposure: a conceptual model describing the mechanisms of stress-induced neurodevelopmental impairment in preterm infants. *Res. Nurs. Health*. **42** (1), 61–71 (2019).
3. Duerden, E. G. et al. Association of early skin breaks and neonatal thalamic maturation a modifiable risk? *Neurology* **95** (24), E3420–E3427 (2020).
4. Duerden, E. G. et al. Early procedural pain is associated with regionally-specific alterations in thalamic development in preterm neonates. *J. Neurosci.* **38** (4), 878–886 (2018).
5. Lavanga, M. et al. The effect of early procedural pain in preterm infants on the maturation of electroencephalogram and heart rate variability. *Pain* **162** (5), 1556–1566 (2021).
6. Ranger, M. et al. Neonatal Pain-related stress predicts cortical thickness at age 7 years in children born very preterm. *PLoS One*. **8**(10). (2013).
7. Smith, G. C. et al. Neonatal intensive care unit stress is associated with brain development in preterm infants. *Ann. Neurol.* **70** (4), 541–549 (2011).
8. Taylor, H. G. & Clark, C. A. Executive function in children born preterm: risk factors and implications for outcome. *Semin. Perinatol.* **40** (8), 520–529 (2016).
9. Aarnoudse-Moens, C. et al. *Meta-analysis of Neurobehavioral Outcomes in Very Preterm and/or Very Low Birth Weight Children* 717–728 (Pediatrics, 2009).
10. van Houdt, C. A. et al. Executive function deficits in children born preterm or at low birthweight: a meta-analysis. *Dev. Med. Child. Neurol.* **61** (9), 1015–1024 (2019).
11. Ansell, J. M. et al. Executive function assessment in New Zealand 2-year olds born at risk of neonatal hypoglycemia. *PLoS One*. **12** (11), e0188158 (2017).
12. O'Meagher, S. et al. Risk factors for executive function difficulties in preschool and early school-age preterm children. *Acta Paediatr.* **106** (9), 1468–1473 (2017).
13. Sentenac, M. et al. Maternal education and cognitive development in 15 European very-preterm birth cohorts from the RECAP Preterm platform. *Int. J. Epidemiol.* (2021).
14. Feldman, R. Mother-infant skin-to-skin contact (kangaroo care)—theoretical, clinical, and empirical aspects. *Infants Young Child.* **17** (2), 145–161 (2004).
15. Feldman, R., Rosenthal, Z. & Eidelman, A. I. Maternal-preterm skin-to-skin contact enhances child physiologic organization and cognitive control across the first 10 years of life. *Biol. Psychiatry*. **75** (1), 56–64 (2014).
16. Gao, H. et al. Effect of repeated Kangaroo Mother Care on repeated procedural pain in preterm infants: a randomized controlled trial. *Int. J. Nurs. Stud.* **52** (7), 1157–1165 (2015).
17. Zvara, B. J. et al. Associations between parenting behavior and executive function among preschool-aged children born very preterm. *Early Child. Res. Q.* **48**, 317–324 (2019).
18. Singer, L. T. et al. Effects of infant risk status and maternal psychological distress on maternal-infant interactions during the first year of life. *J. Dev. Behav. Pediatr.* **24** (4), 233–241 (2003).
19. Statistics, U. I. *International Standard Classification of Education: ISCED 2011* 30 (Comparative Social Research, 2012).
20. Miles, M. S., Funk, S. G. & Carlson, J. Parental Stressor Scale: neonatal intensive care unit. *Nurs. Res.* **42** (3), 148–152 (1993).
21. Biringen, Z., Robinson, J. & Emde, R. *Appendix B: The emotional availability scale (3rd ed.; an abridged infancy/early childhood version)*. 2010: Attachment and Human Development. 256–270.
22. Ainsworth, M. D. S., Blehar, M. C., Waters, E. & Wall, S. N. *Patterns of Attachment: A Psychological Study of the Strange Situation*, 1st ed. (Psychology Press, 2015).
23. Van den Brande, A. et al. Executive function assessment in 2-year-olds born preterm. *Neuropediatrics* **55** (1), 16–22 (2024).
24. Carlson, S. M. Developmentally sensitive measures of executive function in preschool children. *Dev. Neuropsychol.* **28** (2), 595–616 (2005).
25. Kochanska, G., Murray, K. T. & Harlan, E. T. Effortful control in early childhood: continuity and change, antecedents, and implications for social development. *Dev. Psychol.* **36** (2), 220–232 (2000).
26. Zelazo, P. D., Reznick, J. S. & Spinazzola, J. Representational flexibility and response control in a multistep multilocation search task. *Dev. Psychol.* **34** (2), 203–214 (1998).
27. 2019., I. C. R. *IBM SPSS Statistics for Windows, Version 26.0.* (2019).
28. Schlatterer, S. D., du, A. J. & Plessis Exposures influencing the developing central autonomic nervous system. *Birth Defects Res.* **113** (11), 845–863 (2021).
29. Davis, M., Bilms, J. & Suveg, C. Sync and in control: a meta-analysis of parent-child positive behavioral synchrony and youth self-regulation. *Fam. Process.* **56** (4), 962–980 (2017).
30. Diamond, A. Executive functions. *Annu. Rev. Psychol.* **64**, 135–168 (2013).
31. Pascal, A. et al. Neurodevelopmental outcome in very preterm and very-low-birthweight infants born over the past decade: a meta-analytic review. *Dev. Med. Child. Neurol.* **60** (4), 342–355 (2018).
32. Fernandez-Baizan, C. et al. The association between perinatal and neonatal variables and neuropsychological development in very and extremely low-birth-weight preterm children at the beginning of primary school. *Appl. Neuropsychol.-Child*. **10** (4), 348–358 (2021).
33. Ribner, A. et al. Mothers' and fathers' executive function both predict emergent executive function in toddlerhood. *Dev. Sci.* **25** (6), e13263 (2022).
34. Lawson, G. M., Hook, C. J. & Farah, M. J. A meta-analysis of the relationship between socioeconomic status and executive function performance among children. *Dev. Sci.* **21**(2). (2018).
35. Duleep, H. O. The family investment model: a formalization and review of evidence from across immigrant groups. *Gend. Issues*. **16**, 84–104 (1998).
36. Vrantsidis, D. M. C., Chevalier, C. A. C., Espy, N. & Wiebe, S. A. K. A. Socioeconomic status and executive function in early childhood: exploring proximal mechanisms. *Dev. Sci.*. **23**(3). (2020).
37. Grunau, R. E. et al. Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants. *Pain* **143** (1–2), 138–146 (2009).

38. Hodel, A. S. Rapid infant prefrontal cortex development and sensitivity to early environmental experience. *Dev. Rev.* **48**, 113–144 (2018).
39. Paredes, M. F. et al. Extensive migration of young neurons into the infant human frontal lobe. *Science*. **354**(6308). (2016).
40. Galea, M., Park, T. & Hegadoren, K. Improving mental health outcomes of parents of infants treated in neonatal intensive care units: a scoping review. *J. Neonatal Nurs.* **28** (5), 327–334 (2022).
41. Power, J. et al. Maternal perinatal depression and child executive function: a systematic review and meta-analysis. *J. Affect. Disord.* **291**, 218–234 (2021).
42. Priel, A. et al. Maternal depression impairs child emotion understanding and executive functions: the role of dysregulated maternal care across the first decade of life. *Emotion* **20** (6), 1042–1058 (2020).
43. Farroni, T., Della Longa, L. & Valori, I. The self-regulatory affective touch: a speculative framework for the development of executive functioning. *Curr. Opin. Behav. Sci.*. **43**. (2022).
44. Darmstadt, G. L., Kirkwood, B. & Gupta, S. WHO global position paper and implementation strategy on kangaroo mother care call for fundamental reorganisation of maternal–infant care. *Lancet* **401** (10390), 1751–1753 (2023).
45. Broomell, A. P. R. et al. Context of maternal intrusiveness during infancy and associations with preschool executive function. *Infant Child Dev.* **29**(5), e2162 (2020).
46. Clark, C. A. & Woodward, L. J. Relation of perinatal risk and early parenting to executive control at the transition to school. *Dev. Sci.* **18** (4), 525–542 (2015).
47. Spruijt, A. M. et al. Attentional control and executive functioning in school-aged children: linking self-regulation and parenting strategies. *J. Exp. Child. Psychol.* **166**, 340–359 (2018).
48. Bernier, A. et al. A Secure Base from which to regulate: attachment security in Toddlerhood as a predictor of executive functioning at School Entry. *Dev. Psychol.* **51** (9), 1177–1189 (2015).
49. Bernier, A. et al. Social factors in the development of early executive functioning: a closer look at the caregiving environment. *Dev. Sci.* **15** (1), 12–24 (2012).
50. Matte-Gagne, C. et al. Attachment security and developmental patterns of growth in executive Functioning during Early Elementary School. *Child Dev.* **89** (3), E167–E182 (2018).
51. Regueiro, S., Matte-Gagne, C. & Bernier, A. Patterns of growth in executive functioning during school years: contributions of early mother-child attachment security and maternal autonomy support. *J. Exp. Child Psychol.* **200** (2020).
52. Wolke, D., Eryigit-Madzwamuse, S. & Gutbrod, T. Very preterm/very low birthweight infants' attachment: infant and maternal characteristics. *Arch. Dis. Childh.-Fetal Neonatal Ed.* **99**(1), F70 (2014).
53. Browne, J. V. Infant mental health in intensive care: laying a foundation for social, emotional and mental health outcomes through regulation, relationships and reflection. *J. Neonatal Nurs.* **27** (1), 33–39 (2021).
54. Als, H. et al. NIDCAP improves brain function and structure in preterm infants with severe intrauterine growth restriction. *J. Perinatol.* **32** (10), 797–803 (2012).
55. Yrjola, P. et al. Facilitating early parent-infant emotional connection improves cortical networks in preterm infants. *Sci. Transl. Med.* **14**(664). (2022).
56. McAnulty, G. et al. School age effects of the newborn individualized developmental care and assessment program for medically low-risk preterm infants: preliminary findings. *J. Clin. Neonatol.* **1** (4), 184–194 (2012).
57. McAnulty, G. et al. School-age effects of the newborn individualized developmental care and assessment program for preterm infants with intrauterine growth restriction: preliminary findings. *BMC Pediatr.* **13**, 25 (2013).
58. Patronick, J. et al. Parenting interventions targeting behavior for children born preterm or low birth weight: a systematic review. *J. Pediatr. Psychol.* **48** (8), 676–687 (2023).
59. Meuwissen, A. S. & Carlson, S. M. Fathers matter: the role of father parenting in preschoolers' executive function development. *J. Exp. Child. Psychol.* **140**, 1–15 (2015).
60. van Houdt, C. A. et al. Effects of executive function training on attentional, behavioral and emotional functioning and self-perceived competence in very preterm children: a randomized controlled trial. *Front. Psychol.* **10**, 2100 (2019).

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Declarations

Competing interests
The authors declare no competing interests.

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