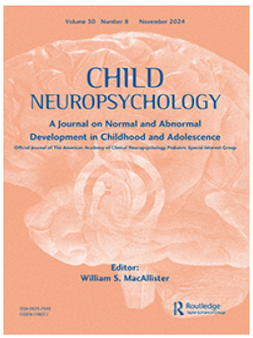

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Relationships between cortisol levels across early childhood and processing speed at age 4.5 years in children born very preterm

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ABSTRACT

Children born very low gestational age (VLGA, 29–32 weeks gestational age [GA]) display slower processing speed and altered hypothalamic pituitary adrenal (HPA) axis function, with greater effects in those born extremely low gestational age (ELGA; 24–28 weeks GA). We investigated trajectories of HPA axis activity as indexed by cortisol output and patterns across cognitive assessment at ages 1.5, 3 and 4.5 years, comparing children born ELGA and VLGA and associations with 4.5-year processing speed. In a prospective longitudinal cohort study, infants born very preterm (<33 weeks gestation) returned for developmental assessment at ages 1.5, 3, and 4.5 years. At each age, children completed standardized cognitive testing and saliva samples collected before (Pretest), during (During) and after (End) challenging cognitive tasks were assayed for cortisol. For the total group ($n = 188$), cortisol area under the curve with respect to ground (AUCg) decreased, while cortisol reactivity to challenge (Pre-test to During) increased from 1.5 to 3 years, remaining stable to 4.5 years. This longitudinal pattern was related to higher Processing Speed (WPPSI-IV) scores at 4.5 years. Children born ELGA displayed higher AUCg than VLGA, particularly at age 3, driven by higher Pre-test cortisol levels. Overall, relative to those born VLGA, children born ELGA displayed greater cortisol responsivity to cognitive challenge. A higher setpoint of cortisol levels at age 3-years in children born ELGA may reflect altered HPA axis regulation more broadly and may contribute to difficulties with information processing in this population, critical for academic and social success.

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Stress; preterm; cortisol; cognition; processing speed

Characterizing the progression from early markers of vulnerability through to subsequent difficulties in functional domains related to mental health problems across the life course is a key objective of clinicians and researchers in developmental psychology and psychiatry. It

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is also a priority of the National Institutes of Mental Health 2022 strategic plan (NIMH, 2023). Children born very preterm (<33 weeks gestation) display a behavioral phenotype of inattention, social withdrawal, poorer social competence and anxiety (Fitzallen et al., 2020). Difficulties in basic information processing abilities, termed "processing speed," have been shown to contribute to poorer development of complex cognitive functions and academic success (Rose et al., 2008; Rose, Feldman & Jankowski, 2011; Rose, Feldman, Jankowski & Van Rossem, 2011), as well as emotional and behavioral problems (Cook et al., 2018; Mulder et al., 2011a, 2011b) in this population.

Regulation of stress hormones via the hypothalamic pituitary adrenal (HPA) axis acts as a primary mediator of long-term effects of early life adversity on later cognition and mental health, across species (Lupien et al., 2009). Infants born very preterm are hospitalized for weeks to months in the neonatal intensive care unit (NICU), exposed ex-utero to significant environmental adversity during the fetal period characterized by rapid development of neuroendocrine systems and brain cytoarchitecture. Frequent exposure to invasive procedures in the NICU induces pain-related stress and involves a cascade of physiological responses that are associated with poorer neurodevelopment and behavior long-term, even after accounting for clinical factors related to prematurity (for review see Grunau et al., 2021). While much research has focused on understanding altered brain maturation associated with preterm birth in relation to later cognitive abilities, few studies have examined of the relationship between physiological stress and cognition. Relationships between basal cortisol and attention in infancy (Tu et al., 2007) and inattention and poorer memory at school-age (Lowe et al., 2023). In an independent cohort, we found that lower IQ at 8-years was related to greater stress reactivity across a cognitive challenge for children born very preterm with the BNDF Met allele (Chau et al., 2017). In the current study we extend prior work to examine, for the first time to our knowledge, relationships between cortisol levels across early childhood and later processing speed at age 4.5 years in children born very preterm. Further understanding of this relationship may help explain individual differences in core cognitive processes that contribute to phenotypic preterm behaviors.

In line with the Adaptive Calibration Model (Del Giudice et al., 2011), environmental exposures in the NICU are related to development of HPA axis activity in children born very preterm (<33 weeks gestation). In infants born preterm (<37 weeks gestational age), during the NICU stay and across the first 6 months, diurnal pattern and cortisol response to stressors appear to be blunted, possibly a result of chronic activation of the HPA axis (Bolt et al., 2002; Grunau et al., 2005; Stoye et al., 2022). Interestingly, a switch to hyper-reactivity is evident in later infancy and toddlerhood. Among the handful of studies to investigate HPA axis activity in children born very preterm, we have shown, across two cohorts, that at age 1.5 years, compared to their full-term counterparts, they display elevated cortisol levels prior to cognitive challenge, particularly those born extremely low gestational age (ELGA; 24–28 weeks gestation [GA]), suggesting altered HPA regulation (Brummelte et al., 2011; Grunau et al., 2005; McLean et al., 2023). Of note, in infancy and toddlerhood, programming of the HPA axis appears to be related to degree of prematurity, with those born ELGA displaying the most significant variation from full-term (Brummelte et al., 2011; McLean et al., 2023; Stoye et al., 2022), while preterm children born closer to term (29–36 weeks) typically display cortisol levels similar to full-terms (Brummelte et al., 2011; Ginnell et al., 2022; McLean et al., 2023; Stoye et al., 2022). We

are aware of only two studies that have investigated HPA axis activity and responsiveness in early childhood in this population. Both studies suggest that, by four to six years, cortisol levels in response to developmental assessment appear to be independent of gestational age at birth (Watterberg et al., 2018) and adverse NICU exposures (McLean et al., 2021). Early childhood is a period of pronounced developmental plasticity of stress-sensitive physiological systems (Hensch & Bilimoria, 2012), development of neurocircuitry associated with stress, fear and regulatory responses (e.g., salience, attention, executive control and default mode networks) (Bruchhage, Ngo, Schneider, D'Sa, & Deoni, 2020), and exposure to new environments (e.g., daycare, kindergarten). However, findings from cross-sectional studies in children born very preterm provide limited understanding of developmental changes in HPA axis activity and responsiveness across early childhood; longitudinal research is needed. Moreover, we do not know how persistent alterations in HPA axis activity relate to core cognitive processes across early childhood in children born very preterm. This is a critical gap in our understanding of the etiology of academic and behavior difficulties in children born very preterm, given that chronic stress has been shown to alter brain maturation of frontal and limbic regions central to regulation of the HPA axis and cognitive functioning (Lupien et al., 2009; VanTieghem et al., 2021).

Understanding the neurodevelopmental sequelae of very preterm birth is critical; however, studies at single time points treat development as static. Assessment of physiological stress reactivity is difficult in early childhood due to ethical constraints. Therefore, in our work, we examine patterns and levels of cortisol across age-appropriate developmental testing in a clinic environment, such that both the unfamiliar setting and the cognitive tasks are challenging for very preterm children (Grunau et al., 2003, 2013; Whitfield et al., 1997).

Here, in a prospective longitudinal cohort study, we examined relationships among degree of prematurity, child cortisol levels and patterns of cortisol secretion across cognitive challenge in children from early childhood to school entry, and with processing speed at age 4.5 years. In the current study, we:

(1) Characterised trajectories of HPA axis activity and responsiveness as indexed by cortisol levels and patterns during developmental testing across ages 1.5, 3, 4.5 years in children born very preterm;
(2) Investigated whether HPA axis trajectories differed for children born ELGA and VLGA;
(3) Investigated whether processing speed at 4.5 years is related to trajectories of physiological stress regulation across age.

Material and methods

Participants and procedures

In a prospective, longitudinal study, $n = 234$ children were recruited from the Level III Neonatal Intensive Care Unit (NICU) at BC Women's Hospital in Vancouver, Canada, between 2006 and 2013. Written informed parental consent was obtained at recruitment, with written re-consent at each study visit. In the

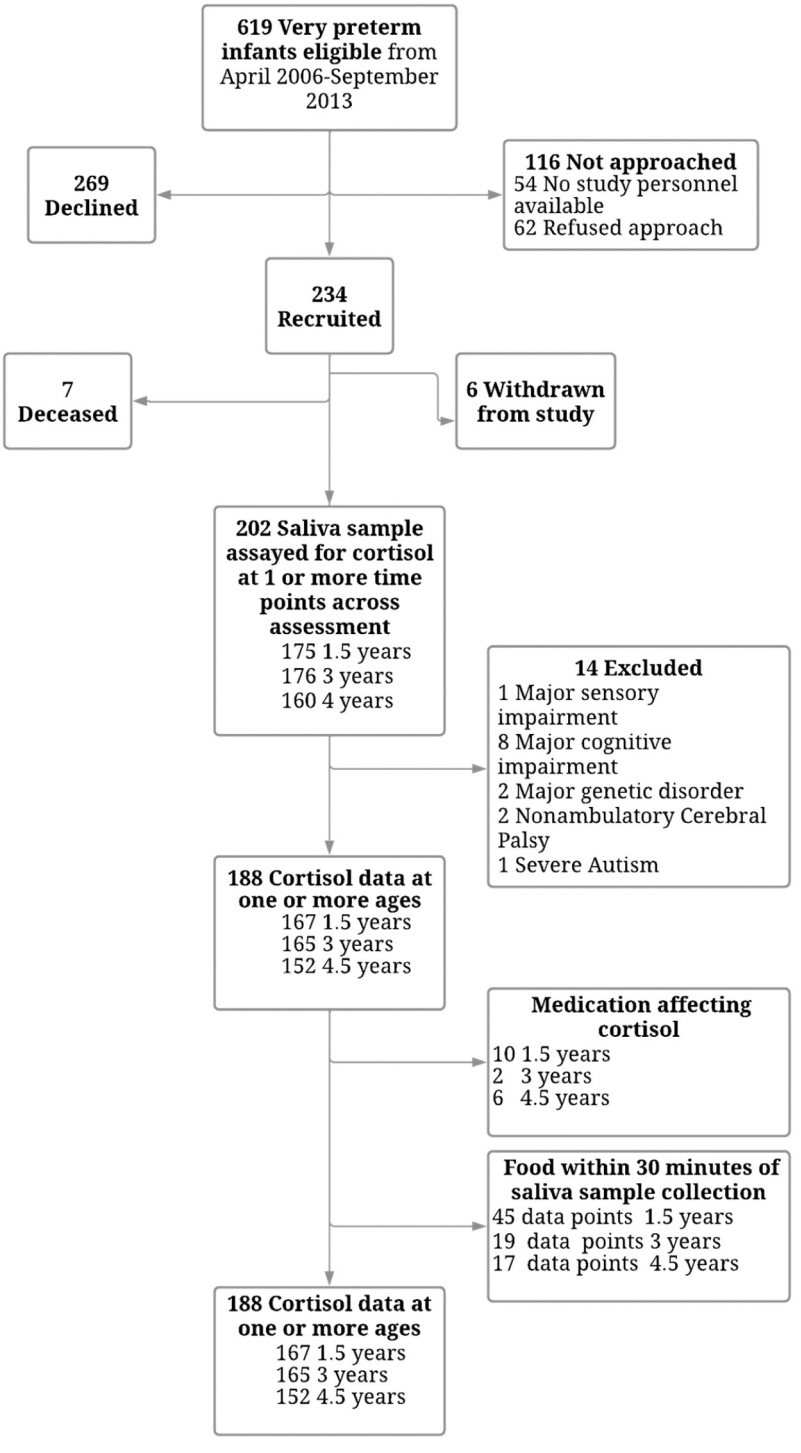

Figure 1. Participant flow chart.

current study, a subset of 188 children (121 ELGA [24–28 weeks GA], 67 VLGA [29–32 weeks GA]) who attended developmental assessment at ages 1.5 ($n = 167$), 3 ($n = 165$) or 4.5 years ($n = 152$) were included; see Figure 1 for flowchart of participant inclusion and exclusions. At each visit, neurodevelopmental assessment was carried out by experienced staff (physiotherapist, psychologist, or developmental consultant) in the Neonatal Follow-up Program at BC Women's Hospital. A caregiver is present during the neurodevelopmental assessment at each age. Saliva samples were collected at three time points on the study day (for collection times at each age, see Supplementary Table S1). Pretest samples were collected after children were settled following arrival at the center. The second sample was collected after children completed age-appropriate cognitive assessment. The final sample was collected at completion of the developmental assessment, approximately 30 minutes after the end of the cognitive assessment (Supplementary Table S1). The study was approved by the University of British Columbia Clinical Research Ethics Board and the BC Children's and Women's Hospitals Research Ethics Board (H05-70579) and was conducted in accordance with the Declaration of Helsinki (1964).

Measures

Neonatal clinical factors and demographics

Medical and nursing chart review was conducted by a neonatal research nurse, including but not limited to: birth weight, gestational age, illness severity (Score for Neonatal Acute Physiology, SNAP II on day 1; Richardson et al., 2001), cumulative pain/stress (number of invasive procedures), cumulative morphine exposure adjusted for daily weight, days on mechanical ventilation, confirmed infection, number of surgeries during NICU stay).

Neurodevelopmental assessment

Child neurodevelopment was assessed at ages 1.5 and 3 years using Bayley Scales of Infant and Toddler Development 3rd Edition (Bayley-III (Bayley, 2005); and at 4.5-years the Wechsler Preschool and Primary Scale of Intelligence- IV (WPPSI-IV).

Child cortisol

As described in procedures, saliva samples were collected at three time points across study visit (Pre-test, During, and End) using salivettes (Salimetrics LLC, State College, PA). Cortisol levels reflect stress levels 20–30 min after an event. Therefore, we interpret Pre-test levels, taken approximately 15 minutes after arrival, to be indicative of cortisol prior to arrival and during cortisol levels to capture levels during cognitive assessment. End saliva samples, taken 20–30 mins after completion of the cognitive assessment (Supplementary Table S1) reflect cortisol levels at end of cognitive assessment prior to other tasks.

Saliva samples were stored at −20°C and assayed using the Salimetrics High Sensitivity Salivary Cortisol Enzyme Immunoassay Kit for quantitative determination of salivary cortisol. All samples were assayed in duplicate. The intra- and inter-assay coefficients of

variation were 5.04 and 6.58 respectively. We examined cortisol patterns across assessment as well as Area Under the Curve with respect to ground (AUCg).

Processing speed at 4.5 years

At the 4.5-year assessment, child processing speed was measured via the WPPSI-IV Processing Speed Index (PSI) score; $M = 100$, $SD = 15$ Scores from two subtests, Bug Search and Cancellation, were used to derive the PSI. Both tasks are completed within a certain time limit. In the Bug Search task, the child marks the bug that matches the target in a larger group. In the Cancellation task, the child scans two arrangements of pictures and marks target objects.

Statistical analysis

Analyses were conducted in R (version 4.1.6; R Core Team, 2015). Physiological data were log transformed, and outliers for cortisol values were winsorized (Miller & Plessow, 2013). Group differences (ELGA and VLGA) in demographic, clinical, and outcome variables were tested with t-tests for continuous variables and chi-square for categorical variables. Hypotheses were tested via a series of multilevel models using *lme4* (Bates et al., 2015) and *lmerTest* (Kuznetsova et al., 2017) R packages. Multilevel models account for within- and between-participant level variance in outcome. Random effects of participant were included in each model as well as random effects of child age and Time Point, dependant on model fit. Model estimates were tested using Restricted Maximum Likelihood Estimation and Satterthwaite method of degrees of freedom (Satterthwaite, 1946). Models accounted for time of day for cortisol collection. All model results are reported with 95% confidence intervals (CI).

Results

Demographics

Neonatal characteristics and demographic indicators are shown in Table 1. Of the 188 children included in the current study, 150 children (94 ELGA [24–28 weeks GA], 82 males) had WPPSI-IV Processing Speed Index scores at 4.5 years. Compared to the VLGA [29–32 weeks GA] group (M = 106.9, $SD = 11.4$, range = 78–128) group, the ELGA group (M = 102.8, $SD = 11.4$, range = 78–132) scored, on average, 4.1 points lower on WPPSI-IV Full Scale IQ ($p = .028$). Similarly, the ELGA group (M = 94.28, $SD = 13.32$) scored significantly lower on the Processing Speed Index than the VLGA group (M = 101.86, $SD = 11.34$, $p = <.001$), more than half a SD lower, which is clinically significant. It is noteworthy that Processing Speed Index scores were more than half a *SD* lower than FSIQ scores (Mdiff = −8.26 (95%CI [−9.87, −6.62]), $p < .001$).

Aim 1. Characterising cortisol output and patterns in response to cognitive challenge across ages 1.5, 3, 4.5 years

As shown in Figure 2, for the total group, the pattern of cortisol output across assessment was similar at 1.5, 3, and 4.5 years, although levels varied across age, F (4, 806.23) = 5.10,

Table 1. Cohort descriptives.

	ELGA (n = 121) Mean (SD) Range (min - max)	VLGA (n = 67) Mean (SD) Range (min - max)	p value
Maternal age at birth (years)	32.0 (5.0) 21.8–44.3	33.1 (5.6) 22.8–45.9	.198
Maternal marital status, n %			.091
Married/Common Law	110 (95)	58 (88)	
Single/Divorced/Separated	6 (5)	8 (12)	
Maternal Level of Education, n %			.186
Partial or Complete Undergraduate Degree	83 (72)	41 (63)	
Post-Graduate University degree	16 (14)	16 (25)	
Primary or Secondary School Graduation	17 (15)	8 (12)	
Gestational age at birth (weeks)	26.6 (1.3) 24.0–28.9	30.6 (1.0) 29.0–32.3	<.001
Child sex at birth (male), n %	63 (52)	37 (55)	.678
Antenatal corticosteroids (exposed)a, n %	104 (86)	49 (73)	.494
Postnatal dexamethasone (days)	3.27 (6.61) 0.0–84.0	0 (0) 0.0–0.0	<.001
Postnatal hydrocortisone (days)	4.59 (12.2) 0.0–31.0	0.15(0.88) 0.0–6.0	<.001
Number of invasive procedures	151.7 (78.3) 26–385	61.5 (30.5) 14–181	<.001
SNAP-II	15.8 (13.6) 0.0–57.0	7.5 (8.1) 0.0–42.0	<.001
Morphine Exposure (dose [mg] adj. daily body weight)	6.3 (12.0) 0.0–58.3	0.6 (3.7) 0.0–29.9	<.001
Days on respiratory support	68.2 (29.4) 0.0–111.0	12.4 (13.2) 0.0–49.0	<.001
Number of Surgeries, median	1 0.0–4.0	0 0.0–3.0	<.001
Culture positive postnatal infection, n %	80 (67)	12 (18)	<.001

[a]intrapartum dexamethasone or betamethasone.

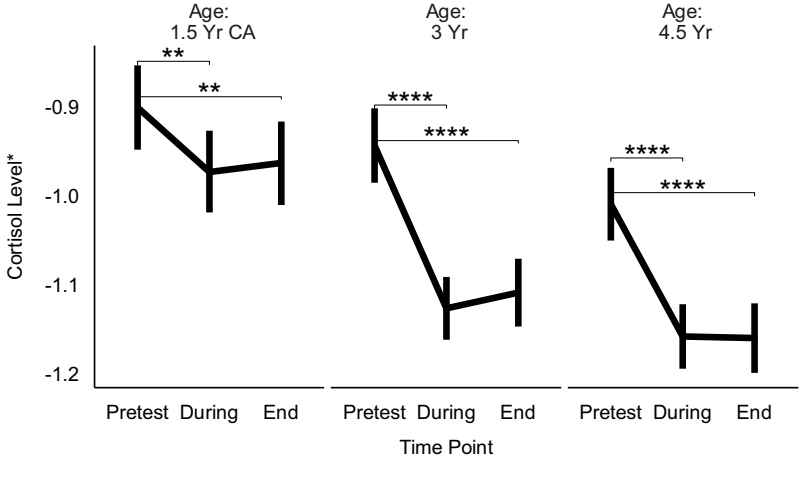

Figure 2. Pattern of cortisol output in response to cognitive challenge across 1.5, 3, and 4.5 years. Log transformed values, **$p < .01$, ****$p < .0001$; Error bars represent 95% confidence interval.

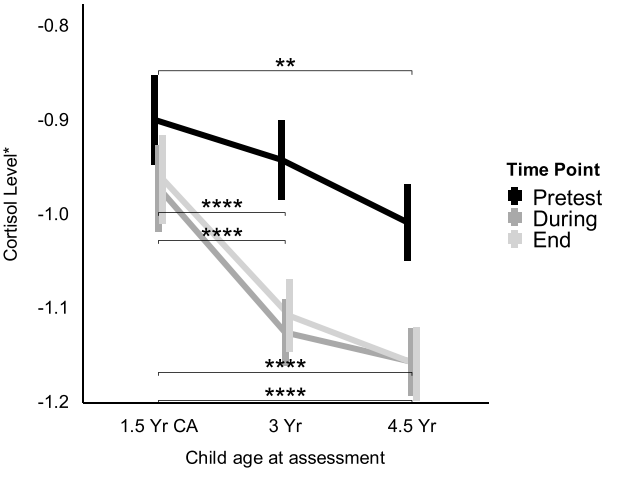

Figure 3. Age-related change in cortisol levels at each time point across assessment. Log transformed values, **$p < .01$, ****$p < .0001$; Error bars represent 95% confidence interval.

$p < .001$. In line with our prior work (Brummelte et al., 2011; McLean et al., 2020), at each age cortisol levels decreased from Pre-test to During, followed by no change through End. At 1.5 years, children displayed a flatter cortisol slope (from Pre-test to During ($B = -0.072$, $SE = 0.02$, $t(969) = -3.15$, $p = .002$), compared to at ages 3 ($B = -0.18$, $SE = 0.02$, $t(1092) = -8.01$, $p < .001$) and 4.5 years ($B = -0.15$, $SE = 0.02$, $t(1089) = -6.11$, $p < .001$). Cortisol change from During to End did not differ across age, $p's > .05$. The pattern of change in cortisol levels from Pretest to During and During to End was the same at 3 and 4.5 years, $p = .191$ and $p = .493$ respectively.

As shown in Figure 3, cortisol levels decreased at During ($B = 0.15$, $SE = 0.03$, $t(333) = 5.44$, $p < .001$) and End ($B = 0.15$, $SE = 0.03$, $t(341) = 5.10$, $p < .001$) from age 1.5 to 3 years. Pre-test levels did not differ at 1.5 and 3 years ($B = 0.04$, $SE = 0.03$, $t(349) = 1.49$, $p = .298$), but dropped significantly from 3 to 4.5 years ($B = 0.07$, $SE = 0.02$, $t(441) = 2.88$, $p = .012$).

Aim 2: cortisol pattern and total output across ages 1.5, 3, 4.5 years in relation to degree of prematurity

Figure 4 displays cortisol levels and patterns within and across 1.5, 3 and 4.5 years separately for children born ELGA and VLGA. Overall, children born ELGA displayed greater cortisol output than children born VLGA ($B = -0.05$, $SE = 0.02$, $t(142.09) = -2.03$, $p = .044$), driven by differences at age 3 years (interaction of GA group x Age $p = .043$; $B = -0.11$, $SE = 0.04$, $t(335) = -2.97$, $p = .003$), see Figure 4(a). The ELGA group showed a decrease in total cortisol output from 1.5 to 3 years ($p = .026$) (although this difference was no longer significant following correction for multiple comparisons ($B = -0.08$, $SE = 0.03$, $t(262) = -2.32$, $p = .055$)), followed by a significant decrease from 3 to 4.5 years ($B = -0.08$, $SE = 0.03$, $t(227) = -2.62$, $p = .026$) (Figures 3(b)). In contrast, the VLGA group showed a steeper decrease in cortisol output from 1.5 years to 3 years ($B = 0.13$, $SE = 0.04$, $t(223) = 3.37$, $p = .003$), followed by no change to 4.5 years

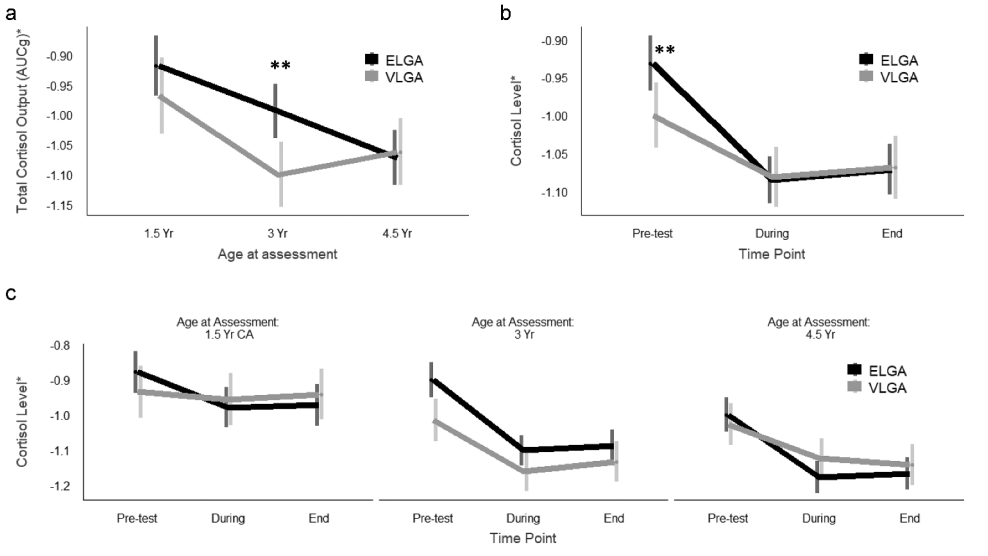

Figure 4. Panel a: total cortisol output across 1.5, 3, and 4.5 years in children born ELGA and VLGA. Panel b: average pattern of cortisol levels across assessments for ELGA and VLGA children. Panel c: pattern of cortisol levels across assessment at each age for ELGA and VLGA children. *Log transformed values, **$p < .01$; error bars represent 95% confidence interval.

($p = .536$), resulting in an overall decrease from 1.5 to 4.5 years ($B = -0.09$, $SE = -0.04$, $t(213) = 2.29$, $p = .047$) (Figure 4(a)). By 4.5 years, no difference in cortisol output between the ELGA and VLGA groups was evident ($p = .780$) Figure 4(a)).

Moreover, ELGA and VLGA groups displayed a different pattern across age, $F(2, 801.28) = 6.27$, $p = .002$), such that ELGA children had higher Pre-test levels ($B = 0.07$, $SE = 0.02$, $t(321) = 2.77$, $p = .006$) and a steeper slope from Pre-test to During (ELGA: $B = 0.15$, $SE = .02$ vs. VLGA: $B = .08$, $SE = .03$; difference in slopes was significant, $B = -0.07$, SE = 0.02, $t(795) = -3.05$ $p = .002$)), see Figure 4(b). Cortisol pattern was consistent across ages for ELGA and VLGA groups (Age x Time Point x GA group, $p = .919$), see Figure 4(c).

Aim 3: trajectories of cortisol in relation to 4.5 year processing speed

Total cortisol output across development was related to 4.5 year WPPSI-IV Processing Speed Index scores ($F(124.38) = 3.64$, $p = .029$), see Figure 5. An initial decrease in cortisol from 1.5 to 3 years ($B = -0.15$, $SE = -0.04$, $t(126) = -3.57$, $p = .007$), with no further change from 3 to 4.5 years ($p = .971$) was associated with higher processing speed (+1SD above the standardized mean). In contrast, a continued decrease in cortisol from 1.5 through 4.5 years ($B = -0.18$, $SE = -0.03$, $t(118) = -5.62$, $p < .001$) was related to lower processing speed (−1SD below the mean). Findings did not differ by GA group. Importantly, total cortisol output was not related to FSIQ across ages ($p = .063$).

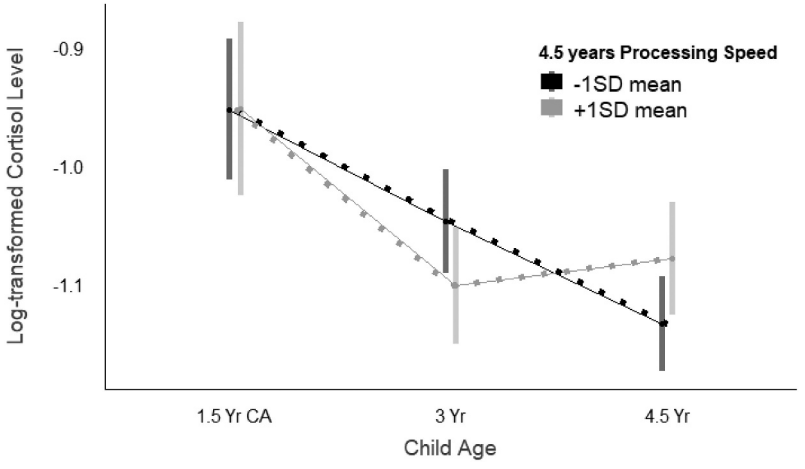

Figure 5. WPPSI-IV processing speed index scores at 4.5 years in relation to AUCg across ages 1.5, 3 and 4.5 years. *Log transformed values; Error bars represent 95% confidence interval.

Discussion

Processing speed is a core neuropsychological factor contributing to cognitive abilities and phenotypic behaviors in children born very preterm (Adrian et al., 2020; Bogičević et al., 2020). Moreover, children born very preterm show altered HPA activity and regulation. However, no empirical work, to our knowledge, has examined longitudinally whether physiological stress regulation across early childhood is related to degree of prematurity and processing speed at school entry. The current study sought to address these gaps. In a prospective longitudinal cohort, with repeated assessment of salivary cortisol output, we characterized the development of physiological stress regulation indexed by salivary cortisol output both prior to and following cognitive challenge at 1.5, 3, and 4.5 years in children born very preterm. We examined whether cortisol levels and patterns within and across ages differed for those born ELGA and VLGA and the relationship between cortisol trajectories and processing speed at 4.5 years.

At each age, children displayed elevated cortisol levels prior to testing, followed by a decrease during assessment and stable levels through to the end of testing. A greater drop in cortisol from pretest to during was evident at 3 and 4.5 years compared to 1.5 years. Across ages, children born ELGA displayed higher cortisol at pretest and a greater drop in cortisol in response to cognitive challenge than children born VLGA. Total cortisol output across ages also differed for the ELGA relative to VLGA group. ELGA children displayed no change in cortisol output from age 1.5 to 3 years, followed by a decrease at 4.5 years. In contrast, overall, children born VLGA showed a decrease in total cortisol output from age 1.5 to 3 years, with no further change from 3 to 4.5 years. A trajectory of decreasing cortisol output was related to poorer processing speed at 4.5 years, while those with above average processing speed abilities at 4.5 years showed an initial decrease in cortisol levels from 1.5 through 3 years, followed by no change through 4.5 years. Together with findings that children born ELGA displayed greater difficulties

in processing speed at age 4.5 years, our findings suggest that altered trajectories of cortisol output across early childhood may contribute to processing speed difficulties. Few studies have investigated physiological parameters in relation to cognitive functioning in this vulnerable very preterm population. Our findings contribute substantively to our understanding of both the evolving nature of physiological stress regulation and the development of processing speed as a core cognitive ability related to phenotypic behaviors in children born very preterm.

Developmental trajectory of cortisol output across ages 1.5, 3, 4.5 years

Typically, comparison of physiological stress responses in studies across childhood is difficult due to methodological differences between studies including type of stressor paradigm (Bonapersona et al., 2022). In the present study, the stressor consisted of coming to an unfamiliar environment, the laboratory, and undergoing an age-appropriate cognitive challenge. Utilizing a unique longitudinal cohort study of children born very preterm, here we examined cortisol levels in repeated saliva samples across cognitive challenge at ages 1.5, 3 and 4.5 years. At all three ages, prior to cognitive assessment, the children displayed high cortisol levels followed by a decrease during assessment, with cortisol levels remaining stable through end of assessment. We have now shown this same cortisol pattern in response to a developmentally appropriate cognitive challenge across two independent cohorts of children born very preterm (Brummelte et al., 2011, 2015; McLean et al., 2019, 2023). While psychosocial stressors typically elicit an increase in cortisol levels, in our prior work at 1.5 years, full-term children also show a decrease from pretest to during assessment; however, cortisol levels were significantly lower at pretest in full-term children compared to children born very preterm (Brummelte et al., 2011; McLean et al., 2023).

Interestingly, while novelty is thought to evoke a cortisol increase, evidence from early studies of HPA axis functioning demonstrated decreases in cortisol to novel and engaging situations in infancy and preschool (Gunnar & Donzella, 2002). We interpret elevated cortisol levels among the very preterm children prior to testing as anticipatory anxiety reflecting heightened wariness to an unfamiliar situation (Poole & Schmidt, 2021). Future research utilizing this test paradigm could examine observed behavioral correlates of this cortisol pattern.

Independent of degree of prematurity, children displayed elevated cortisol levels and a flatter slope during cognitive challenge at 1.5 years in comparison to later ages from toddlerhood through preschool years, children showing normative development show greater stability of diurnal rhythm and decreasing levels of baseline cortisol levels (Watamura et al., 2004). In our present study, a greater drop in cortisol levels across cognitive challenge at 3 and 4.5 years, double that which occurs at 1.5 years, could similarly be indicative of development of stress response systems. Studies of normative samples have demonstrated both adaptivity to stressors and continued development of physiological stress system responses including heightened HPA axis responses (Rudd et al., 2021) and ongoing autonomic nervous system development through preschool age (Alkon et al., 2014). Indeed, across these ages, children transition from a relatively low-stress environment at home to exploring new environments, engaging in social play, and being cared for by alternate caregivers at daycare, preschool, and kindergarten.

Moreover, from infancy through early childhood, maturational shifts in higher-order brain networks (Bruchhage et al., 2020) and attention processing (Rueda et al., 2013), drive a shift from exogenous (bottom-up) to endogenous (top-down) regulatory strategies. A greater cortisol drop across cognitive challenge could therefore also be due to increased ability to exert endogenous control over orienting toward the challenging cognitive task. Increased use of cognitive and behavioral self-regulatory strategies may facilitate adaptive physiological responses and thus provide positive feedback loops in later toddlerhood and into the preschool years (Ursache et al., 2012).

Taken together, our longitudinal work and the (limited) cross-sectional research conducted to-date suggest that the developmental trajectory of HPA axis responsiveness and regulation in children born very preterm is non-linear. Following a period of blunted cortisol levels during the NICU stay through early infancy, we found here that children born very preterm show hyper-reactivity to novelty in late infancy, and that this response increases in magnitude through toddlerhood and early childhood. We postulate that, in line with theoretical models of stress response system development (Boyce et al., 2021; Del Giudice et al., 2011), the non-linear trajectory evident in the very preterm population is suggestive of early "programming" of HPA axis functioning in the sensitive period of early life followed by heightened responsivity to external environmental cues across early childhood.

Stress system development in early childhood is particularly responsive to environmental influences and co-regulated by caregivers during these early years (Brummelte et al., 2011; Gunnar & Donzella, 2002). Given parents of preterm children self-report that their own stress remains elevated after NICU discharge of their infant (Gray et al., 2018) and the important role of parents in social co-regulation of HPA axis activity (Gunnar & Donzella, 2002), it is perhaps surprising that children do not continue to display dampened cortisol responses and profiles. However, it is possible that parent-infant physiological co-regulation increases by the time children are 1.5 years of age resulting in some degree of normalization in cortisol stress responses. Indeed, prior work suggests that those exposed to positive parent–child interactions (Brummelte et al., 2011) and caregiver regulatory feedback (Provenzi et al., 2016) display more normative cortisol levels. In future research, we aim to examine the role of parent stress and parent behaviors on child physiological stress across early development.

HPA-axis activity and degree of prematurity

Evidence of long-term alterations of HPA axis functioning following early adversity was evident. First, the pattern of cortisol response to cognitive challenges differed between children born ELGA and those born VLGA across ages. On average, children born ELGA displayed elevated pretest cortisol levels and thus a greater drop from pretest to during assessment. We have previously shown that elevated cortisol levels at baseline and subsequently greater cortisol response to challenge are associated with greater exposure to neonatal pain/stress and clinical factors associated with prematurity at age 1.5 years (Grunau et al., 2007; McLean et al., 2023). Our current findings extend our prior work, suggesting alterations in cortisol response to challenge *across early childhood* are related to the degree of prematurity and programming via adversity during the fetal period ex-utero. Prior research suggests directionality of HPA axis dysregulation is related to the

timing and nature of stress exposure early in life. While exposure to elevated stress in utero is typically related to hyper-reactivity of stress systems (McLean et al., 2020; Yong Ping et al., 2015, 2020), early postnatal adversity is related to hypo-regulation of cortisol across childhood (Koss et al., 2016). Birth at extremely low gestational ages (24–28 weeks) occurs at a time when activation of enzymatic processes occurs and cortisol begins to be released (22–23 weeks gestation; Ishimoto & Jaffe, 2011) and thus likely first affects fetal brain development. At this stage of fetal development, pregnancy insults and birth complications associated with prematurity provoke a cortisol response (Gitau et al., 2001), potentially disrupting early fetal cortisol-brain interactions. Our finding of greater decrease in cortisol levels in response to cognitive challenge, on average, for children born ELGA compared to VLGA, suggests a lack of adaptivity to challenge across early childhood may be due to fetal sensitivity to adversity during this developmental window.

Importantly, developmental trajectories of total cortisol output between ELGA and VLGA groups differed, driven by elevated total cortisol output at 3 years for children born ELGA. Children born VLGA displayed a significant decrease in cortisol output from 1.5 through 3 years, remaining stable through 4.5 years. In contrast, children born ELGA displayed no significant change in total cortisol output through 3-years, followed by a decrease in cortisol output at 4.5 years. As discussed above, an overall decrease in cortisol levels at each assessment time point and thus a decrease in total cortisol output across ages 1.5 through 4.5 years is possibly indicative of a lowering of the homeostatic set-point across this period. Those born ELGA show delayed maturation of HPA axis functioning, related to early adversity. Together, our findings suggest being born extremely preterm is associated with elevated physiological responsivity to unfamiliar situations. Elevated cortisol levels at age 3-years and associated trajectory of cortisol in children born preterm are potentially indicative of delayed maturation and/or adaptivity of the stress response. The nature and timing of stress exposure in early life may induce specific changes in directionality and long-term development of the HPA axis.

Processing speed and HPA-axis activity

A developmental trajectory of HPA-axis activity akin to that of the ELGA group across early childhood was related to poorer processing speed at school entry. Our finding suggests that chronic stress exposure across early childhood may be associated with long-term effects on cognitive abilities in this population. In line with prior literature (van Houdt et al., 2019), in the present study children born ELGA displayed greater processing speed difficulties at age 4.5 years. While poorer processing speed may be related to increased stress as children born very preterm deal with academic pressures and new social interactions, heightened stress, anxiety, and inattention may slow the speed of processing, both in the short and longer term. Indeed, profiles of chronic stress are associated with poorer cognitive and executive functioning across the lifespan (Lupien et al., 2009), even in early childhood (Blair & Berry, 2017; Watamura et al., 2004). Finally, our finding extends research demonstrating relationships between abnormalities in neonatal white matter and deep gray matter and adverse processing speed performances at school-age in children born very preterm (Murray et al., 2014). In the current study, we identified a physiological correlate of a neuropsychological domain that may contribute to phenotypic behaviors and later complex cognitive difficulties in children born very preterm.

Strengths, limitations, and future directions

While longitudinal assessment across early childhood is a significant strength of our study, it is not without limitations. Without a full-term comparison group, we are unable to describe normative patterns of cortisol output in response to the cognitive challenge. However, as noted above, we have previously shown differences in cortisol output across cognitive challenge between full-term born and preterm born children in this same cohort at age 1.5 years (McLean et al., 2023). Due to funding limitations we were not able to follow the full-term children beyond age 1.5 years. Another limitation is that saliva samples were collected in the morning when children attended neonatal follow up clinic visits. However, we accounted for time of day of saliva collection in all analyses, as due to the sharper decline of the cortisol circadian curve toward midday, it is possible that effects of stress on cortisol concentrations are obscured by morning assessment times (Miller et al., 2016; Stalder et al., 2016). Finally, we did not examine cortisol trajectories in relation to enrollment in daycare/preschoon. Given research has demonstrated relationships among socioeconomic status, physiological stress regulation, and child cognition (Blair et al., 2011) future research could look to examine the influence of this environmental factor on the pathway we identified. Finally, research in normative populations in early childhood is beginning to demonstrate the utility of identifying profiles of physiological reactivity across multiple stress systems, specifically the autonomic nervous system and HPA axis, for understanding the development of behavior problems (Rudd et al., 2021). Examination of multisystem physiological reactivity in very preterm children is an exciting potential next step which could provide a multisystem understanding of the nature of physiological regulation in this population.

Conclusions

This is the first study, to our knowledge, to describe trajectories of HPA axis activity across early childhood in children born very preterm. Our results highlight the importance of examining cortisol levels longitudinally across multiple ages to better capture developmental changes in physiological stress regulation. Longitudinal trajectories differed for children born ELGA and VLGA, with children born ELGA displaying higher cortisol output at 3-years. Altered cortisol output across ages related to degree of prematurity may contribute to functional differences in processing speed at 4.5 years in children born very preterm. Our work emphasizes the importance of understanding the nature of child physiological stress regulation in relation to functional outcomes in childhood utilizing longitudinal research designs.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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