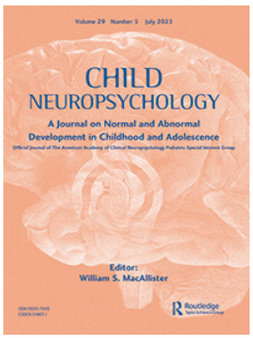

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Neural and behavioral indicators of cognitive control in preschoolers with and without prenatal opioid exposure

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ABSTRACT

Prenatal opioid exposure is one consequence of the opioid epidemic, but effects on child development remain poorly understood. There is emerging evidence that children exposed to opioids in utero exhibit elevated emotional and behavioral problems, which may be partially due to alterations in cognitive control. Using multiple methods (i.e., neuropsychological, behavioral, and event-related potential [ERP] assessments), the present study examined differences in emotional, behavioral, and cognitive control difficulties in preschool-aged children with ($n = 21$) and without ($n = 23$) prenatal opioid exposure ($M_{age} = 4.30$, $SD = 0.77$ years). Child emotional and behavioral problems were measured with a caregiver questionnaire, indicators of cognitive control were measured using developmentally appropriate behavioral (i.e., delay discounting, Go/No-Go) and neuropsychological (i.e., Statue) tasks, and electroencephalogram was recorded to error and correct responses in a Go/No-Go task. ERP analyses focused on the error-related negativity (ERN), an ERP that reflects error monitoring, and correct-response negativity (CRN), a component reflecting performance monitoring more generally. Opioid exposure was associated with elevated difficulties across domains and a blunted ERN, reflecting altered cognitive control at the neural level, but groups did not significantly differ on behavioral measures of cognitive control. These result replicate prior studies indicating an association between prenatal opioid exposure and behavioral problems in preschool-aged children. Further, our findings suggest these differences may be partially due to children with prenatal opioid exposure exhibiting difficulties with cognitive control at the neural level. The ERN is a potential target for future research and intervention efforts to address the sequelae of prenatal opioid exposure.

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Prenatal opioid exposure; cognitive control; error-related negativity; performance monitoring; preschool

The opioid epidemic is a major public health crisis (Lyden & Binswanger, 2019; Substance Abuse and Mental Health Administration Service, 2019; U.S. Department of Health and Human Services, 2021), with widespread impacts, including on infants and

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children exposed to opioids in utero. In the US, approximately 7% of women reported the use of a prescription opioid pain reliever during pregnancy (Ko et al., 2020), and the number of women with opioid-related diagnoses at delivery increased by 131% from 2010 to 2017 (Hirai et al., 2021). Existing studies have found evidence that children with prenatal opioid exposure exhibit a broad range of challenges, including emotional and behavioral difficulties (Bandstra et al., 2010; de Cubas & Field, 1993; Jain et al., 2014; Pulsifer et al., 2008). However, the underlying factors driving these emotional and behavioral difficulties remain unclear.

Children with prenatal opioid exposure may demonstrate elevated emotional and behavioral problems due in part to underlying difficulties in cognitive control. Cognitive control, also referred to as executive function, is the ability to select goals and modulate responses to attain goals, including inhibiting prepotent responses and monitoring performance to adjust behavior (Friedman & Robbins, 2022; National Institute of Mental Health, 2023; Somerville & Casey, 2010). In the present article, we use the term *cognitive control* to be consistent with the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) framework (Insel et al., 2010; National Institute of Mental Health, 2023). Cognitive control tends to improve from infancy through young adulthood (Davidson et al., 2006; Somerville & Casey, 2010). Difficulties with cognitive control are known to play a role in many emotional and behavioral problems, and this is likely an important process to target with early intervention efforts (Carlson & Wang, 2007; Kertz et al., 2016; Miller et al., 2013).

Evidence from observational behavioral studies suggest that prenatal exposure to opioids may disrupt the development of cognitive control, but the neural processes underlying these effects remain unclear. One study examined cognition in infants with and without diagnoses of neonatal opioid withdrawal (NOWS) using the Bayley Scales of Infant and Toddler Development and found that infants with NOWS diagnoses had significantly lower language and cognition scores than age-matched comparison infants (Beckwith & Burke, 2015). Further, there is behavioral evidence of difficulties in cognitive control, specifically, emerging in early childhood after exposure to opioids in utero. For example, a study comparing 4-year-old children with and without histories of prenatal methadone or buprenorphine exposure found that children with prenatal exposure demonstrated lower overall performance on a battery of neuropsychological tests which examined aspects of cognitive control, including shifting, inhibition, and related working memory (Konijnenberg & Melinder, 2015). Previous work also demonstrates that preschool-aged children with histories of prenatal opioid and poly-substance exposure exhibit elevated behavioral problems compared to children without prenatal exposure (Nygaard et al., 2016). Given that disruptions in cognitive control are often associated with elevated emotional and behavioral problems (Brown, 2008; Fitzgerald et al., 2021), alterations in cognitive control may be a key process underlying elevated risk for children with prenatal opioid exposure.

In addition, existing studies using neonatal structural magnetic resonance imaging (MRI) indicate that prenatal opioid exposure may impact the structure of the developing brain during gestation (Sirnes et al., 2017; Yuan et al., 2014), with implications for cognitive control and emotional and behavioral problems. For example, children with prenatal opioid exposure show smaller whole brain and white matter volume, as well as smaller volume in the thalamus – a region which contributes to cognitive control functions (Halassa & Kastner,

2017) – compared to children without exposure (Sirnes et al., 2017; Yuan et al., 2014). There is also evidence that infants with prenatal opioid exposure show greater volume in the right cingulate gyrus, an area of the brain associated with substance use (Merhar et al., 2021). In addition, prenatal opioid exposure may have consequences for brain network development as previous research demonstrates that infants with prenatal exposure demonstrate greater amygdala functional connectivity with the medial prefrontal cortex (Radhakrishnan et al., 2021). The medial prefrontal cortex is critical to cognitive control (Ridderinkhof et al., 2004), suggesting that alterations in these brain networks in infants with prenatal opioid exposure could lead to difficulties in the development of cognitive control and consequential emotional and behavioral problems. Importantly, however, the effects of prenatal substance exposure on brain development may be confounded with exposure to other psychosocial stressors related to caregiver substance use. As such, we need to examine the extent to which the effects of prenatal opioid exposure persist when accounting for factors like socioeconomic status, which is known to also relate to brain and cognitive control development (Hurt et al., 2001; Li et al., 2022).

Growing evidence supports the use of neurophysiological methods to directly measure cognitive control in young children (Ip et al., 2019; Lutz et al., 2021). Specifically, the error-related negativity (ERN) is a response-locked event-related potential (ERP) derived from the electroencephalogram (EEG) that is specifically indicated as a measure of cognitive control in the NIMH RDoC framework (National Institute of Mental Health, 2023; Weinberg et al., 2015). The ERN is generated by the anterior cingulate cortex and emerges over frontocentral sites approximately 0–100 milliseconds after commission of an error on speeded tasks (Gehring et al., 1993, 2018). The ERN is conceptualized to reflect error detection, a necessary component of performance monitoring that then allows for subsequent learning and corrective goal-oriented action (Sutton & Barto, 1998; Thorndike, 1927). Supporting this conceptualization, increased ERN magnitude is associated with more subsequent corrective behaviors, such as greater reaction time and increased rate of correct responses following commission of an error (cite) and decreased ERN magnitude is associated with decreased response control and higher levels of impulsivity and externalizing symptoms (Gehring et al., 1993, 2018). The ERN develops across early childhood and into young adulthood (Kim et al., 2007), with detection of this neural signal in children as young as 3 years of age (Brooker, 2018). ERPs are useful measures of brain activity in early childhood in that they are noninvasive, offer millisecond temporal precision, and are easily administered (Brooker et al., 2020). The ERN specifically has strong properties for assessment of cognitive control in children, as previous research has demonstrated this component to be moderate to high in reliability in children, both within a single assessment and in test-retest reliability across 2 years (Meyer et al., 2014).

To our knowledge, only one prior study has examined ERPs related to performance monitoring in children exposed to opioids in utero, though the ERNwas not included (Konijnenberg et al., 2018). This study examined children's ($N = 40$; aged 9–11 years) performance and stimulus-locked ERPs during a modified flanker task. Children of mothers treated with methadone or buprenorphine during pregnancy ($n = 19$), in comparison to children without prenatal opioid exposure ($n = 21$), demonstrated atypical stimulus-locked ERPs during a flanker task, potentially reflecting difficulty with selective attention (Konijnenberg et al., 2018). Specifically, comparison children exhibited an increased P3 on trials that involved conflict between the targets and distractors compared

to congruent trials. In contrast, children with prenatal opioid exposure did not show P3 modulation as a function of level of conflict. Notably, these analyses did not account for other psychosocial or comorbid factors that are also implicated in the development of these cognitive processes, such as age, sex, and socioeconomic status (Hurt et al., 2001; Li et al., 2009; Rothbart et al., 1994; Somerville & Casey, 2010). Interestingly, children with prenatal opioid exposure did not differ from comparison participants in behavioral performance on the flanker task, which suggests neural measures may elucidate more subtle alterations in cognitive control than observational performance measures in early childhood.

The current preliminary study aimed to examine symptoms of emotional and behavioral problems as well as behavioral and neural (i.e., ERN and correct-response negativity [CRN]) indicators of cognitive control in preschool-aged children with and without prenatal opioid exposure. We hypothesized that children with prenatal opioid exposure would show greater emotional and behavioral problems relative to comparison children. Additionally, we hypothesized that children with prenatal opioid exposure, relative to comparison children, would exhibit more difficulties with cognitive control, as measured by lower performance on neuropsychological and behavioral measures and a reduced ERN.

Method

Participants

Participants were 44 children (21 with and 23 without prenatal opioid exposure based on caregiver reports) aged 3 to 5 years ($M = 51.70$ months, $SD = 9.29$ months; 59% female). In terms of race, caregivers identified participants as White (88%), Black and/or African American (5%), Multiracial or Other Race (5%), and Asian (2%); and, in terms of ethnicity, 5% of children were identified by their caregivers as Hispanic and/or Latinx(e). Participants were recruited from the greater Nashville area through social media advertising on Facebook and Instagram, flyers and brochures posted in physician offices, as well as via distribution of flyers to providers of early intervention services (e.g., Tennessee Early Intervention Services). Caregivers interested in the study completed an online form via REDCap (a secure web application for online surveys and databases; Harris et al., 2019) and were contacted via phone to provide detailed description of the study as well as to conduct a phone screen to confirm eligibility. Prenatal opioid exposure was determined based on caregiver report on an eligibility phone screen. The primary caregiver was required to be at least 18 years of age, a parent or legal guardian of the child, and able to read and speak English fluently. Children with a history of neurological injuries were excluded, along with those whose primary caregiver had any severe learning disabilities that may have interfered with completion of the study tasks. Of the 21 participants with a history of prenatal opioid exposure, 20 had been adopted. All participants without a history of prenatal opioid exposure lived with their biological parent(s). The average age of adoption/foster care was 5.32 months ($SD = 10.97$, range 0–36 months). There was no statistically significant association between age of adoption and most measures of interest in the subset of children who were adopted (age: $r = -.26$, $p = .290$, sex: $r = -.15$, $p = .541$, income-to-needs ratio: $r = .04$, $p = .900$, Statue task standard score: $r = -.24$, $p = .326$, Zoo task accuracy: $r < -.01$, $p = .989$, Zoo task ERN residual: $r = -.48$, $p = .195$, Zoo task correct-response negativity (CRN): $r = -.34$, $p = .367$, Zoo task ERN: $r =$

–.50, $p = .166$, inattention/hyperactivity: $r = –.30$, $p = .205$, defiant/aggressive behavior: $r = .13$, $p = .604$, anxiety: $r = .06$, $p = .795$, mood and affect: $r = .16$, $p = .515$, physical symptoms: $r = .16$, $p = .515$). There was a significant association between age of adoption and delay discounting: $r = .50$, $p = .039$, such that older age at adoption was associated with more selections of immediate rewards. There was also a trend association between age of adoption and Zoo task RT such that older age at adoption was associated with slower RT on correct trials: $r = .57$, $p = .052$.

Procedures

Study procedures were approved by the Vanderbilt Institutional Review Board. Caregiver – child dyads were invited to one laboratory session. Informed consent was obtained from parents and assent was obtained from children. Parents completed an interview about their child's birth history, medical and developmental history, and social and emotional behavior. Parents also completed questionnaires on REDCap while their child completed a neuropsychological assessment battery. Following the neuropsychological assessment battery, children completed a series of EEG tasks in a counterbalanced order. Last, participants completed a delay discounting task to measure cognitive control in emotional contexts (i.e., ability to delay gratification when a larger reward is possible). The study duration was approximately four hours in total. See supplement for all measures included in the study procedures. Caregiver – child dyads were compensated with a $100 gift card for their participation in the study. All data were collected during the COVID-19 pandemic. Due tostay-at-home orders, 14 participants completed portions of the study, including the Statue subtest, through a videoconferencing platform.

Measures

Conners Early Childhood

Caregivers completed the Conners Early Childhood Assessment Parent Report form (Conners, 2009). The Conners provides information regarding a broad range of behavioral, emotional, social, cognitive, and developmental issues in children between the ages of 2 to 6 years. The Conners Early Childhood scales are measured using a 4-point Likert-type scale: "*Not at all true (Never, Seldom)*," "*Just a little true (Occasionally)*, "*Pretty much true (Often Quite a Bit)*," and "*Very much true (Very often, Very frequently)*." In the current sample, internal consistency was good for most scales and ranged from .83 to .96. However, internal consistency for social functioning/atypical was low (.48) and was excluded from our analyses.

Delay discounting task

To assess cognitive control in motivational contexts, children completed a preschool version of a delay discounting task (Hodel et al., 2016) to assess the extent to which they can inhibit drives for immediate reinforcement in order to obtain a higher value delayed reward. Specifically, delay discounting was measured by a brief task using 6 laminated cards demonstrating possible immediate or delayed rewards (e.g., a picture of 1 fruit snack on one side of the card and picture of 2 fruit snacks with a picture of a clock on the other side), consistent with previously developed procedures.

Participants were presented with 6 cards in a random order and prompted to decide between receiving 1 item now (e.g., 1 fruit snack, 1 sticker) or more of these items later (e.g., 2 fruit snacks, 5 stickers). If participants selected now, they received a fruit snack or a sticker immediately. If participants selected later, their items for later were placed in a small cup placed adjacent to the experimenter. Participant selection of immediate rewards were summed across the 6 trials, such that higher values reflect greater tendency to select immediate rewards and greater discounting of the value of delayed rewards.

Statue subtest

To assess cognitive control at the behavioral level using a standardized measure, children completed the Statue subtest from A Developmental NEuroPSYchologocial Assessment (NEPSY-II). The NEPSY-II is a standardized neuropsychological battery validated for children aged 3–16 years that assesses functioning across several domains, including cognitive control (Korkman et al., 2007). For the purposes of this study, we focused only on the Statue subtest, which assesses motor persistence and inhibition in young children. The children are asked to maintain standing body position with eyes closed during a 75-second period and to inhibit impulsive urges to respond to sound distracters (e.g., examiner drops pencil, coughs, mutters). As noted above, 14 participants completed the Statue subtest over a video call, in which cases caregivers were instructed to orient the computer camera to allow the research team member to see the children's full posture during the task. The instructions for the task were identical to those provided to participants that completed the task in the lab space. Statue scores did not significantly differ for those who completed this task virtually ($M = 7.46$, $SD = 4.52$) vs. in person ($M = 7.29$, $SD = 3.63$), $t(42) = 0.13$, $p = .895$, Cohen's $d = .04$.

Zoo task. The Zoo Task is an ERP Go/No-Go task developed and validated for use with young children (Grammer et al., 2014). The premise of the task is that children need to help zookeepers find animals who escaped from the zoo. Participants were instructed to click the left mouse button as quickly as possible when they saw animals to get them back to the zoo and withhold button presses when they saw orangutans who were helping the zookeepers. A higher proportion of images were other animals rather than orangutans, so that the task requires inhibiting a prepotent response. Participants completed a practice block prior to the start of the task. The children then completed 8 blocks of the task, each with 40 trials (each including 10 images of orangutans and 30 novel zoo animal pictures), for a total of 320 trials. Each animal image was preceded by a fixation cross displayed for a randomized interval ranging between 200 and 300 ms. The stimulus was then presented for 750 ms, followed by a blank screen for 500 ms. Responses could be made while the stimulus was on the screen or at any point during the blank screen presentation. Each block consisted of novel sets of animal photographs, and each set was balanced with respect to color, animal type, and size. Of the 44 participants in the sample, 38 completed the Zoo task, with useable EEG data for 29 participants and behavioral data for 34 participants (5 were excluded for not making responses on the task, 4 for having an insufficient number of artifact free trials per condition).

EEG data collection and processing

EEG data were recorded with 16-electrodes using BrainProducts actiCHamp system (Munich, Germany) based on standard 10/20 layout. Of note, a 32-channel cap was used but we selected a subset of 16 channels to reduce the time spent capping in order to maintain participant engagement and minimize close contact during the COVID-19 pandemic (Simmons & Luck, 2020). Impedances were reduced to 10 kΩ. A 24-bit resolution and sample rate of 1000 Hz were used to digitize the recordings. BrainVision Analyzer software (Brain Products, Munich Germany) was used to process the EEG data. Data were referenced to an average of all electrodes and band-pass filtered with 0.1 and 30 Hz as cutoffs. Data were segmented 500 ms prior to and 500 ms after correct responses and errors of commission (i.e., pressing the button on No-Go trials). Automatic artifact rejection criteria were a voltage step greater than 50.0 μV between sample points, the maximum voltage difference of 175 μV with trials, and minimum voltage difference of 0.5 μV within 100 ms intervals. After automatic artifact rejection, data were also inspected visually to reject any remaining artifacts.

Following artifact rejection procedures, participants had on average 107.46 (*SD* = 42.24; range 23–221) correct trials at Fz, 109.50 (*SD* = 39.24; range 35–221) correct trials at Cz, 19.04 (*SD* = 8.85; range 23–221) error trials at Fz, and 19.92 (*SD* = 8.20; range 9–40) error trials at Cz. Prior research indicates that the ERN becomes stable after approximately 6 trials (Meyer et al., 2013; Pontifex et al., 2010). Most participants had 8 or more error trials at both Cz and Fz. However, one child had only 3 trials at Fz. To avoid excluding this participant and maximize the amount of data included, we also conducted analyses with only the Zoo task ERN scored at Cz and results were generally consistent with those reported here. Because results were largely unchanged when we conducted analyses separately at Fz and Cz, we proceeded with pooled frontocentral cites (i.e., Fz, Cz) for our analyses.

ERPs were averaged across responses such that error and correct trials were averaged separately, and baseline corrected from 500 ms prior to responses to 300 ms prior to responses. To examine the ERN, data were extracted between 0 and 100 ms after commission of an error at pooled frontocentral cites (i.e., Fz, Cz), consistent with prior ERN research (Canen & Brooker, 2017; Overmeyer et al., 2021; Riesel et al., 2013; Sandre et al., 2020; Zilong Pang et al., 2016). In addition, the CRN, a component that arises immediately following a correct response, was scored in the same time window and electrode sites. The CRN is a negative deflection in the ERP that typically follows all responses and is theorized to reflect generic response monitoring (Simons, 2010). Therefore, to isolate error-specific neural activity, we used a regression-based procedure to compute unstandardized residuals of the ERN difference (Meyer et al., 2017). To calculate the ERN residuals, participants' CRN was entered as the predictor, the ERN was the dependent variable, and unstandardized residuals were saved.

ERPs in responses to errors minus correct responses and the corresponding scalp distribution are presented in Figure 1. CRN and ERN had high split-half reliability at pooled Fz and Cz sites (r_{SB}= 0.70 and 0.70).

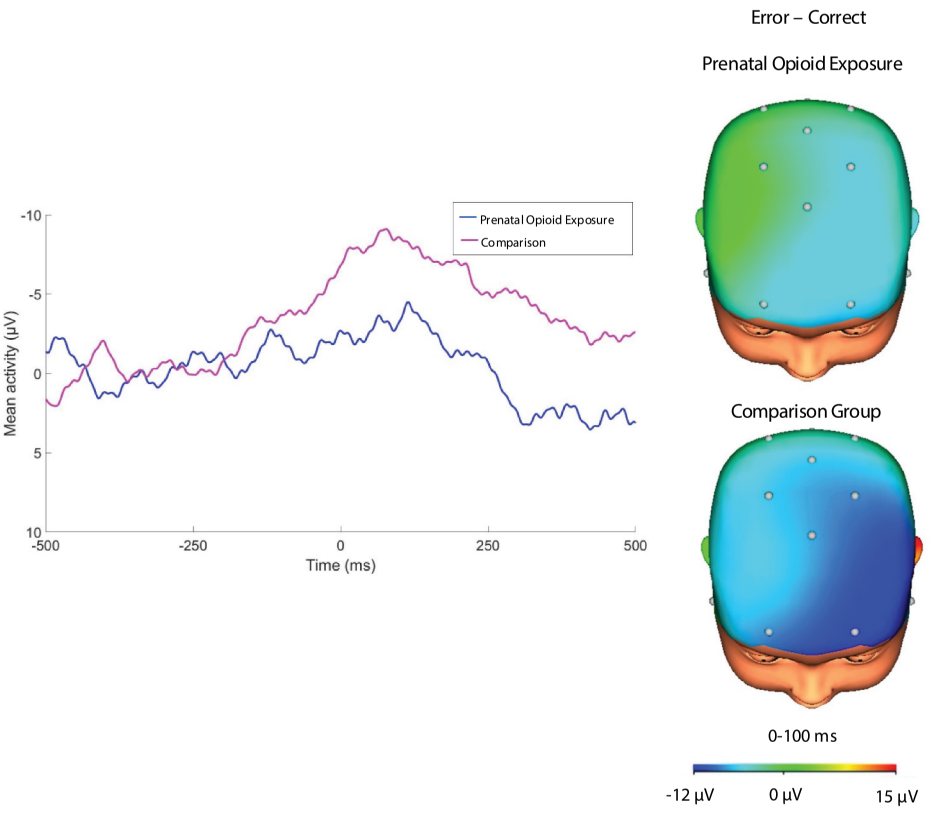

Figure 1. ERP difference waves (error minus correct; negative values plotted up) at pooled sites Fz and Cz and scalp distributions depicting the error minus correct response for each group.

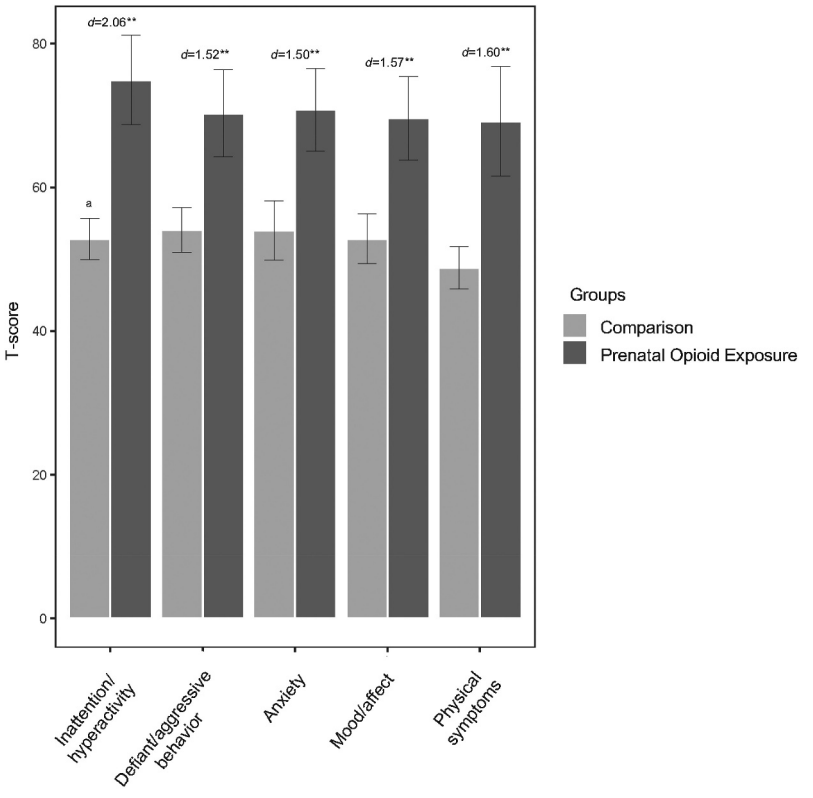

Figure 2. Group means on Conners Early Childhood Behavior scales.
Note. **Difference is significant at the .01 level (2 tailed). [a]Standard error bars.

Data analysis

Prenatal opioid exposure and comparison groups were dummy coded (i.e., comparison group = 0, prenatal opioid exposure group = 1) for all analyses. First, independent samples *t*-tests were conducted to test group differences in emotional and behavior problems (i.e., Conners subscales: inattention/hyperactivity, defiant/aggressive behavior, anxiety, mood and affect, physical symptoms) and behavioral and neural indicators of cognitive control (i.e., delay discounting scores, Statue standard score, Zoo task accuracy, Zoo task reaction time, Zoo task CRN, Zoo task ERN, Zoo task ERN residual). Next, hierarchical linear regression models were conducted to examine whether the effects of prenatal opioid exposure on emotional and behavioral problems and behavioral and neural measures of cognitive control persist when accounting for demographic and psychosocial factors including age, sex, income-to-needs ratio. Previous research links age (Rothbart et al., 1994; Somerville & Casey, 2010), socioeconomic status (Hurt et al., 2001), and sex (Li et al., 2009) with individual differences in cognitive control. We aimed to examine the extent to which opioid exposure group differences persist with these covariates included. All analyses were conducted using R (R Studio version 2022.02.2). We used full-information maximum likelihood to estimate missing data in regression analyses (Enders, 2001) via the lavaan package (Rosseel, 2012).

Results

Descriptive statistics and group differences

Tables 1 and 2 present descriptive statistics including mean, standard deviation, independent samples *t*-tests, and effect sizes for the comparison and prenatal opioid exposure groups across all study variables. Although not statistically significant, the comparison group was relatively older and demonstrated a relatively larger income-to-needs ratio than the prenatal opioid exposure group with a small effect size. In addition, χ^2 tests indicated that there were no significant group differences in child sex, race, or ethnicity, or parental education. Children with prenatal opioid exposure had significantly elevated symptoms on all emotional and behavioral problem dimensions relative to the comparison group with large effect sizes (see Figure 2).

For the Statue subtest, children with prenatal opioid exposure showed relatively lower scores than the comparison children with a small effect size, but group differences were non-significant. In contrast, children with prenatal opioid exposure had no notable differences delay discounting scores compared to the comparison children. For the Zoo task, although the effect was a trend that did not reach statistical significance, the prenatal opioid exposure group demonstrated lower accuracy than the comparison group with a medium effect size. There was no notable difference in RT for correct responses between prenatal opioid exposure group and comparison group. The Zoo task ERN and Zoo task ERN residual were significantly blunted in the prenatal opioid exposure group relative to the comparison group with a large effect size. There was no notable difference in Zoo task CRN between the prenatal opioid exposure group and comparison group.

Regression analyses

We conducted separate hierarchical linear regression models to examine the effects of prenatal opioid exposure on emotional and behavioral problems and measures of cognitive control, accounting for age, income-to-needs ratio, and sex. Prenatal opioid exposure was still significantly associated with inattention/hyperactivity ($\beta = 0.73$, $p = <.001$, CI 95% [0.52, 0.94]), defiant/aggressive behavior ($\beta = 0.60$, $p = <.001$, CI 95% [0.35, 0.85]), anxiety ($\beta = 0.57$, $p = <.001$, CI 95% [0.33, 0.82]), mood and affect ($\beta = 0.60$, $p = <.001$, CI 95% [0.36, 0.85]), physical symptoms, $\beta = 0.66$, $p = <.001$, CI 95% [0.41, 0.91], Zoo task ERN ($\beta = 0.38$, $p = .046$, CI 95% [0.01, 0.76]), and Zoo task ERN residual ($\beta = 0.39$, $p = .044$, CI 95% [0.01, 0.76]).

When covarying for age, sex, and income-to-needs ratio, prenatal opioid exposure was not significantly associated with Statue task standard scores ($\beta = -0.16$, $p = .246$, CI 95% [−0.42, 0.11]), Zoo task reaction time ($\beta = 0.04$, $p = .833$, CI 95% [−0.32, 0.40]), Zoo task CRN ($\beta = <0.01$, $p = .951$, CI 95% [−0.30, 0.32]), or delay discounting scores, $\beta = -0.18$, $p = .456$, CI 95% [−0.67, 0.30]. There was still a trend association with Zoo task accuracy, $\beta = -0.32$, $p = .059$, CI 95% [−0.65, 0.01].

Correlations between measures

Finally, we examined the extent to which the Zoo task ERN, Zoo task CRN, and Zoo task ERN residual correlated with emotional and behavioral problems in the overall sample

Table 1. Independent samples t-tests between the comparison and prenatal opioid exposure groups for continuous study variables.

	Comparison Group		Prenatal Opioid Exposure Group							95% CI of the *M* Difference		
Measure	*M*	*SD*	*M*	*SD*	t	*df*	*p*	*M Difference*	*SE of the M Difference*	*LL*	*UL*	Cohen's *d*
Age (months)	52.22	10.00	51.14	8.65	0.38	42	.706	1.08	2.83	−4.60	6.79	0.12
Income to needs ratio	1.52	0.60	1.38	0.55	0.80	36	.454	0.14	0.19	−0.24	0.53	0.24
Inattention/hyperactivity	52.78	6.67	74.95	13.70	−6.92	42	<.001	−22.17	3.21	−28.64	−15.70	2.06
Defiant/aggressive behavior	54.04	7.22	70.29	13.31	−5.09	42	<.001	−16.24	3.19	−22.68	−9.81	1.52
Anxiety	54.00	9.57	70.81	12.60	−5.01	42	<.001	−16.81	3.36	−23.58	−10.04	1.50
Mood and affect	52.83	8.01	69.62	12.86	−5.25	42	<.001	−16.79	3.20	−23.44	−10.15	1.57
Physical symptoms	48.78	6.82	69.19	16.77	−5.38	42	<.001	−20.41	3.80	−28.07	−12.75	1.60
Delay discounting score	3.58	2.09	3.85	1.79	−0.44	37	.665	−0.27	0.62	−1.53	−0.99	0.27
Statue task standard score	8.37	3.88	6.52	3.89	1.50	38	.142	1.85	1.23	−0.65	4.34	0.48
Zoo task: Accuracy (%)	55.59	11.94	47.70	10.51	1.97	31	.058	0.08	0.04	<-0.01	0.16	0.97
Zoo task: RT to correct (ms)	197.52	41.76	200.70	36.63	−0.23	31	.821	−3.19	13.98	−31.70	25.33	0.08
Zoo task: ERN residual	−2.70	7.07	3.19	6.40	−2.12	22	.046	−5.88	2.78	−11.64	−0.13	0.87
Zoo task: CRN	11.32	2.61	11.77	5.24	−0.27	22	.790	−0.45	1.65	−3.87	2.98	0.11
Zoo task: ERN	3.14	7.01	9.07	6.48	−2.14	22	.044	−5.93	2.78	−11.69	−0.18	0.88

LL = lower limit. UL = upper limit. Zoo Task Accuracy is coded with 0 = incorrect and 1 = correct.

Table 2. Independent samples t-tests between the comparison and prenatal opioid exposure groups for categorical study variables.

	Comparison Group ($N = 23$) M	Prenatal Opioid Exposure Group ($N = 21$) M	df	χ^2	p
Sex (% Male)	.70	.48	1	2.19	.139
Race (% White)	.85	.10	1	2.51	.113
Ethnicity (% Hispanic and/or Latinx)	.02	.00	1	0.934	.334
Primary caregiver college graduate (%)	.82	.71	1	0.68	.409

Sex was coded as 0 = female and 1= male. Race was coded as 0 = Black/African American, Asian, and multiracial identities and 1 = White. College degree was coded as 0 = some college or lower level of education and 1 = college degree or higher.

when covarying for age, sex, and income-to-needs ratio. A blunted Zoo task ERN was associated with greater inattention/hyperactivity, $\beta = 0.54$, $p = .002$, CI 95% [0.20, 0.89]. The Zoo task ERN residual was also positively associated with inattention/hyperactivity, $\beta = 0.54$, $p = .002$, CI 95% [0.19, 0.88]. Other than inattention/hyperactivity, the Zoo task ERN and Zoo task ERN residual were not statistically significantly associated with emotional or behavioral problems (ps > .127). The Zoo task CRN was not statistically significantly associated with any symptom dimension.

Discussion

In the present preliminary study, we used a multimethod approach to examine emotional and behavioral problems and behavioral and neural indicators of cognitive control in preschool-aged children with and without prenatal opioid exposure. Consistent with prior research (Beckwith & Burke, 2015; Maguire et al., 2016), we found that children with prenatal opioid exposure exhibited greater emotional and behavioral problems across domains compared to children with no reported prenatal opioid exposure. Second, we found a blunted neural response to errors (i.e., Zoo task ERN, Zoo task ERN residual) in children with prenatal opioid exposure, indicating decreased error monitoring, a key component of cognitive control. Finally, there was a trend for children with prenatal opioid exposure to exhibit lower accuracy on the Zoo task, although overall the effects of opioid exposure on behavioral measures of cognitive control did not reach significance.

In the current study, we extended work demonstrating associations between prenatal opioid exposure and emotional and behavioral problems in children (Beckwith & Burke, 2015; Maguire et al., 2016). A longitudinal study comparing children with and without prenatal exposure to opiates and poly-substances found that the exposed group exhibited significantly more problems in several behavioral areas, particularly with regard to attentional problems (Nygaard et al., 2016). In line with previous work, prenatal opioid exposure in our sample was associated with broad-scale symptoms in preschool age children, including both externalizing and internalizing symptoms, with large effects as measured on Conners subscales. Taken together, these findings indicate that preschool-aged children prenatally exposed to opioids may be at increased risk for functionally impairing emotional and behavioral problems.

Another key finding from the current study centers on the association between prenatal opioid exposure and the Zoo task ERN. Children with prenatal opioid exposure exhibited both an attenuated ERN and ERN residual compared to children without prenatal

exposure, reflecting decreased error monitoring in those with prenatal opioid exposure. As expected, attenuated error monitoring, as measured by the ERN and ERN residual, was associated with greater inattention and hyperactivity. This is consistent with the conceptualization of the ERN as a possible endophenotype for externalizing symptoms (Heffer & Willoughby, 2021; Lutz et al., 2021; Olvet & Hajcak, 2008). Interestingly, prior research demonstrates that an attenuated ERN is commonly associated with decreased response inhibition and greater commission of errors (Schwager & Rothermund, 2013); however, in our small sample, prenatal opioid exposure was not statistically significantly associated with task-based behavioral indicators of cognitive control. It is important to note that children with prenatal opioid exposure did demonstrate a trend toward lower accuracy on the Zoo task relative to the comparison group with a moderate effect size and that neural – behavioral associations are not always observed in the literature, even in the context of significant associations between attenuated ERN and greater externalizing symptoms (Heffer & Willoughby, 2021). Overall, the significant group differences specifically for the Zoo task ERN, and not behavioral measures, indicate neural measures may provide unique insight into more subtle alterations in processing beyond what is observable behaviorally. It is important to note, however, that effect sizes for prenatal opioid exposure on neural measures were relatively smaller than the effect sizes for symptoms of emotional and behavioral problems provided via caregiver report. As such, it is recommended future studies continue to use multiple methods in investigating the effects of prenatal opioid exposure on child outcomes.

Importantly, research on other forms of prenatal substance exposure has indicated that associated psychosocial factors may confound the effects of prenatal substance exposure on development (Hurt et al., 2001). In the present study, we attempted to address these potential confounds by statistically controlling for household income-to-needs ratio, and the associations between prenatal opioid exposure with inattention/hyperactivity, defiant/aggressive behavior, mood and affect, physical symptoms, and the ERN remained significant. It is important to note, however, that we were not able to account for all aspects of children's early environments that may influence cognitive control. In particular, nearly all children in the opioid exposure group were adopted, compared to none of the children in the comparison group. Familial placement changes may influence observed effects on symptoms and cognitive control (Kendler et al., 2015; Merz et al., 2013), and we were unable to examine this possibility with the present sample. Further, we did not have information on adopted children's biological parents and were unable to covary for psychosocial factors associated with children's biological families such as biological parents' income-to-needs ratio or other forms of substance use or psychopathology. In the present sample, children in the prenatal opioid exposure group were most often adopted at birth, and as such, income-to-needs of the adoptive parents' home may best be considered as characteristics of the children's post-birth context.

In future work on the impact of prenatal opioid exposure on child development, it will be important to carefully consider confounds by selecting comparison groups that better isolate the effects of prenatal substance exposure specifically. Most children in the opioid exposure group for the current study were adopted. Thus, to directly compare the effects of opioid exposure on cognitive control, there is a need for methods to more carefully characterize and measure early environmental experiences. Further, given elevated

behavioral problems in the opioid exposure group, it may be helpful to compare to children with similar levels of behavioral problems but no known opioid exposure to determine the extent to which there may be distinct underlying patterns of brain function between these groups.

Several other limitations of the current study should be noted. First, although our sample size is consistent with prior studies of prenatal opioid exposure (Beckwith & Burke, 2015; Konijnenberg et al., 2018) and reflect the challenges of this research, small samples can produce biased estimates (Button et al., 2013). The present study contributes to a growing body of work with this difficult to recruit population, and results should be considered as preliminary. Second, the nature of substance exposure in humans does not allow for random assignment. Therefore, we were unable to use a causal comparative design, considered the gold standard for identifying direct links for an outcome following an exposure. Third, we relied on caregiver report for information about history of substance exposure and did not have access to birth records to verify exposures and diagnoses. In addition, we do not have detailed information about the duration, severity, and chronicity of opioid and polysubstance use histories of birth parents during pregnancy. It is likely that outcomes of prenatal opioid exposure are highly heterogenous and more research on these specific factors is needed. Fourth, the measures of interest and analytical approach were not preregistered. Fifth, it is important to note that there may be differences between adoptive parents who did and did not express interest in an opioid exposure study, such that those with elevated emotional and behavioral problems and concerns about their child may be more likely to seek out opportunities to participate in research. Finally, although the present study focuses on cognitive control, there are many other processes to study in future research on prenatal opioid exposure, including memory, language skills, and emotional and reward processing. More comprehensive assessments will be needed to elucidate areas in which children exposed to opioid in utero are likely to need additional supports, as well as identifying areas of strengths.

Conclusion

Given the dramatic increase in the prevalence of prenatal opioid exposure in recent years (Hirai et al., 2021), there is a need to better understand the degree to which there are neural, behavioral, and functional effects of prenatal opioid exposure on young children. The present study is a critical step in understanding the effects of prenatal exposure across these domains using rigorous multimodal assessment. Our results indicate that prenatal opioid exposure is associated with elevated emotional and behavioral problems in preschool age children. It is important to note, however, that we were unable to account for confounds like prenatal exposure to other substances or other maternal co-occurring mental or physical health conditions, which should be considered in future research. In addition, prenatal opioid exposure was associated with attenuated error monitoring at the neural level, even when covarying age, sex, and income-to-needs ratio. Taken together, these findings indicate that exposure to opioids in utero could have impacts on children's cognitive control and functioning into the preschool years, highlighting the need for continued support for pregnant people to help to reduce opioid use and early intervention efforts to promote healthy development in infants and children exposed to opioids.

Disclosure statement

The authors complied with ethical standards in the treatment of participants. The study was approved by the Vanderbilt University Institutional Review Board and all procedures were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. Written consent was obtained from the parents of all participants. Verbal assent was obtained from all participants. The material reported in this manuscript is original, not previously published, and not under concurrent consideration elsewhere. The authors have no conflicts of interest to disclose with regard to the submitted work.

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