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# Substance use and mothers' neural responses to infant cues

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**ABSTRACT**

Substance use may influence mothers' responsiveness to their infants and negatively impact the parent–infant relationship. Maternal substance use may co-opt neural circuitry involved in caregiving, thus reducing the salience of infant cues and diminishing the sense of reward experienced by caring for infants. Gaps in understanding exist with regard to the mechanisms by which substance use operates to influence mothers' processing of infant cues and how this translates to caregiving. Therefore, we examined how substance use might relate to maternal neural responses to infant cues using event-related potentials (ERPs). Substance-using ($n$ = 29) and nonsubstance-using ($n$ = 29) mothers viewed photographs of infant faces and heard recordings of infant vocalizations while electroencephalography was recorded simultaneously. Three specific ERP components were used to examine initial processing of infant faces (N170) and cries (N100), and attentional allocation to infant faces and cries (P300). Substance-using mothers did not discriminate facial affect at early encoding stages (N170), were generally slower to orient to infant cries (N100), showed heightened responses to neutral faces (P300), and failed to adaptively differentiate between high-distress versus low-distress cries (P300). These differences may be important to caregiving behaviors associated with the formation of mother–child attachment. Implications are discussed, as are limitations and future directions.

**KEYWORDS**

EEG/ERP, infant cues, mothers, substance use

## 1 | INTRODUCTION

Substance use is a significant public health concern. The rise in substance use by perinatal women is especially concerning given the potentially deleterious consequences for infants. The National Survey on Drug Use and Health (NSDUH) showed that between 2015 and 2016, estimates of illicit drug use by pregnant women aged 15 to 44 years increased from 4.7% to 6.3% (Substance Abuse and Mental Health Services Administration, 2017). Substance use during pregnancy may have direct teratogenic effects on the developing fetus and thereby may exert multigenerational effects. Given that polysubstance use is common among mothers who use substances, the impact of prenatal exposure may be varied. Prenatal exposure to illicit substances may contribute to Neonatal Abstinence Syndrome (NAS; Kellogg, Harms, Rose, & Watson, 2011), physical birth defects (Broussard, Rasmussen, Reefhuis, Friedman, Jann, Riehle-Colarusso, & Honein, 2011), executive functioning concerns, visuoperceptual integration problems (Wu, Jew, & Lu, 2011), and motor delays (Pujol et al., 2004). In addition, substance use during pregnancy may co-occur with high levels of maternal stress, which may contribute to shortened gestational age, preterm birth, low birth weight, and small size relative to gestational age (Class, Lichtenstein, Långström, & D'Onofrio, 2011), as well as poorer infant attention regulation and cognitive development (Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2002; Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003), and externalizing problems in toddlerhood (Gutteling et al., 2005).

Substance use may also impact infant development indirectly via effects on maternal caregiving behaviors including decreased caregiver sensitivity (Mayes & Truman, 2002), poorer reflective capacity (Suchman, DeCoste, Castiglioni, Legow, & Mayes, 2008; Suchman, DeCoste, Leigh, & Borelli, 2010), and insecure parent–child attachment relationships (Mirick & Steenrod, 2016; Quinlivan & Evans, 2005). These caregiving differences contribute in part to the high rate of child welfare involvement experienced by mothers who use substances (Eiden, Foote, & Schuetze, 2007; Taplin & Mattick, 2015). For example, substance-using mothers are significantly more likely to have an infant removed from their care compared to mothers who do not use substances (U.S. Department of Health and Human Services, 1999).

Key neural circuits that are involved in caregiving have also been implicated in stress and reward processing (Rutherford, Williams, Moy, Mayes, & Johns, 2011). Critically, these circuits may be dysregulated in substance-using mothers, resulting in a neurobiological profile that may compromise caregiving behaviors. The "reward–stress dysregulation model" (Rutherford & Mayes, 2017; Rutherford, Potenza, & Mayes, 2013) posits that reward–stress neural circuits that are disrupted by addiction provide a neurobiological pathway for understanding how substance use compromises caregiving processes. Functional magnetic resonance imaging (fMRI) has identified neural activation in brain regions related to caregiving behavior (e.g., reward, motivation, and cognitive control) and identified differences in substance-using versus nonsubstance-using mothers with respect to infant affective stimuli. In particular, infant affective faces (i.e., happy, neutral, and sad) elicited a relatively blunted response in substance-using mothers' prefrontal regions, visual processing regions, and limbic regions of the brain, as compared to nonsubstance-using mothers. Infant emotional cries (i.e., high-distress and low-distress) elicited a similar neural pattern, with substance-using mothers demonstrating reduced neural activation in prefrontal regions, auditory sensory processing regions, and limbic regions (Landi et al., 2011). These results extended to mothers' neural responses to their own infants' faces, with substance-using mothers demonstrating reduced activation of dopamine- and oxytocin-innervated brain regions (i.e., hypothalamus, ventral striatum, and medial prefrontal cortex) when shown images of their own smiling infants (Kim et al., 2017). Such results provide neurobiological support for mechanisms by which maternal substance use may co-opt neural circuits involved in caregiving, which may in turn lead to decreased salience of infant cues, diminished responsiveness to infants, and lessened sense of reward experienced by engaging in caregiving behaviors.

Electroencephalography (EEG) and event-related potentials (ERPs), in addition to fMRI, may further elucidate mothers' neural responses to infant cues. EEG has greater temporal specificity relative to fMRI, and using EEG, activation within certain brain regions associated with rewards experienced by viewing infant faces occurs at the approximate time (in milliseconds) in which an ERP indicating structural encoding of infant faces occurs (Jantzen et al., 2017). Overall, studies utilizing EEG/ERP allow researchers to measure very rapidly unfolding responses to infant cues, thereby providing detailed information regarding the stages of infant-cue detection and processing (Maupin, Hayes, Mayes, & Rutherford, 2015). This information has been linked to reward processing (Jantzen et al., 2017), maternal behavior toward their own children (Endendijk, Spencer, van Baar, & Bos, 2018), and reflective functioning (Rutherford, Maupin, Landi, Potenza, & Mayes, 2017b; Rutherford et al., 2018).

EEG data may be gathered via electrodes that measure voltages generated by postsynaptic potentials of cortical pyramidal neurons via the electrodes' placements at specific scalp locations. These data may be visualized as waveforms. When EEG data are time-locked to a task or stimulus event and averaged across multiple trials of stimulus presentation, ERPs may be generated and permit visualization of clearly defined positive (P) and negative (N) peaks. These peaks are considered indices of sensory (e.g., auditory and visual) and cognitive (e.g., attention) processes. The waveforms may show with considerable precision the magnitude (i.e., amplitude in microvolts) and timing (i.e., latency in milliseconds) of neural responses to stimuli.

Specific ERP waveform components (i.e., positive or negative peaks) may provide insight into neural responses to stimuli. Given that crying is a predominant way in which infants communicate their needs very early in life, mothers' abilities to initially register and process these auditory cues are vital to the development of parent–child relationships. The N100, a negative waveform peak occurring at approximately 100 ms following the onset of a sound, may provide insight into the auditory processing of infant cues. This ERP component may be especially informative for caregiving research given that recently postpartum mothers evidence stronger N100 responses to infant vocalizations compared to a control group of women (i.e., women who were not pregnant, did not have children under 2.5 years of age, and did not have an occupation related to child care; Purhonen, Valkonen-Korhonen, & Lehtonen, 2008). In fact, recently postpartum mothers also demonstrated greater N100 responses to neutral stimuli compared to control women, suggesting that new mothers have generally increased alertness to auditory information (Purhonen et al., 2001).

The N170, the negative peak occurring at approximately 170 ms after an image is presented, may provide important insight into the visual processing of faces. Although visual processing begins as early as the P100, the N170 is specific to facial structural encoding (Batty & Taylor, 2003; Bentin, Allison, Puce, Perez, & McCarthy, 1996; Eimer, & Holmes, 2007). Notably, the amplitude (but not the latency) of the N170 response is affected by the perceived reward of the face that is presented, with more rewarding faces triggering a greater N170 amplitude (Marini, Marzi, & Viggiano, 2011). Given that infant faces are typically experienced as rewarding (as evidenced by activating dopamine-associated reward-processing regions of the brain including the nucleus accumbens; Glocker et al., 2009; Hahn & Perrett, 2014; Strathearn, Li, Fonagy, & Montague, 2008), it is not surprising that individuals demonstrate significantly larger N170 responses to infant faces compared to adult faces (Colasante, Mossad, Dudek, & Haley, 2017).

Later ERP components (e.g., P300, N/P600, late positive potential or LPP) have been used to examine individuals' attentional engagement and cognitive evaluation of stimuli (Ritter & Ruchkin, 1992). With regard to infant cues, all adults regardless of gender or parental status tend to demonstrate the strongest P300 response to highly distressed infant faces compared to infant faces showing pleasure, comfort, or discomfort (Proverbio, Brignone, Matarazzo, Del Zotto, & Zani, 2006), suggesting increased attentional allocation to highly negative emotions relative to neutral or positive emotions. Further, compared to nonparents, both mothers and fathers demonstrate larger P300 responses in response to infant faces of various emotional expressions (particularly distress). Proverbio et al. (2006) suggest that with parenthood comes increased salience of infant cues, a finer encoding of infant emotions, and a more acute ability to attend to infant suffering. These factors may result in greater parental sensitivity that induces appropriately empathic caregiving responses to intense emotions. Examined further, the largest P300 was exhibited by mothers (compared to fathers and nonparents of both genders) in response to highly negative infant cues, with these results representing one example of the biological differences in mothers that may be associated with hormonal changes during pregnancy and childbirth (Proverbio et al., 2006).

Recently, researchers have examined the potential effects of tobacco smoking on the timing and strength of mothers' neural responses to infant cues, with overall results suggesting that neural responses (measured by ERPs) are impacted by smoking status. Specifically, compared to nonsmoking mothers, tobacco-smoking mothers exhibited delayed N170 responses to infant faces (of all emotional expressions studied), suggesting slower visual processing and decreased salience or reward value of infant cues (Rutherford, Maupin, Landi, Potenza, & Mayes, 2017a). Additionally, the strength (i.e., amplitude) of tobacco-smoking mothers' P300 responses varied by facial expression (strongest for neutral faces), whereas this was not the case for nonsmoking mothers. These results indicate that tobacco-smoking mothers may be utilizing greater attentional resources when viewing neutral faces, which may be related to increased effort expended to cognitively evaluate these faces due to their ambiguity. In contrast, tobacco-smoking status did not relate to mothers' responses to infant cries (Rutherford et al., 2017a).

Our study extends this previous work on maternal neural responses by examining how substance use status (other than tobacco-smoking) may affect maternal processing, perception, and attention to auditory and visual cues of various infant emotions. To do so, we examined mothers' electrocortical response (ERPs) to cries of varying distress levels and to faces displaying different emotions (e.g., happy, sad, and neutral) in substance-using mothers (see substance-use information below) relative to a group of demographically matched mothers who did not use substances previously or at the time of their participation in the current study. Cry and face stimuli were taken from infants not known by the mothers.

Given previous research indicating reduced saliency of infant cues (cries and faces) in substance-using mothers (Landi et al., 2011), as well as findings that tobacco-smoking mothers show differential ERP responses to infant faces (Rutherford et al., 2017a), we predicted that substance-using mothers would demonstrate slower initial processing of infant cues as well as differential levels of attentional responding based on infants' emotional expression. Specifically, we hypothesized that substance-using mothers would show longer N100 latency and similar N100 amplitude in response to infant cries, and longer N170 latency and similar amplitude in response to infant faces. We additionally predicted that substance-using mothers would demonstrate greater strength (i.e., larger amplitude) of P300 responses to neutral infant faces and cries of all types. Such findings would have implications related to intervention targets for this population.

## 2 | METHODS

### 2.1 | Participants

Recently postpartum ($M = 8.19$ weeks, $SD = 6.86$ weeks) mothers were recruited and screened for substance use as part of a larger study. Twenty-nine substance-using mothers between the ages of 18 and 42 years inclusive ($M = 28.03$, $SD = 5.72$) participated. Maternal substance use was assessed as previously reported in Landi et al. (2011) via self-report measures as well as a short version of the Addiction Severity Index (ASI-Lite; McLellan, Luborsky Woody, & O'Brien, 1980). Mothers were classified as substance-using if they indicated current or previous problematic substance use in adulthood (e.g., cannabis, heroin, methadone, other opiates, barbiturates, sedatives, cocaine, amphetamines, hallucinogens, and inhalants), having used any teratogenic substances during the second and/or third trimesters of pregnancy, or having participated (currently or previously) in substance-use treatment in adulthood. Twenty-nine nonsubstance-using mothers (i.e., endorsed no current or past substance use) between the ages of 18 and 43 years inclusive ($M = 29.07$, $SD = 6.61$) participated in the study and were used as a control comparison group (yielding a total sample of 58 participants). Control participants were demographically matched based on ethnicity, education (in years), parity (primiparous and multiparous), and maternal age. Groups differed with respect to marital status, though given that we did not have information regarding whether unmarried mothers were in committed relationships, marital status was not included as a covariate and is included here solely for descriptive purposes. See Table 1 for participant demographic information. Yale University's Human Investigation Committee approved all procedures prior to recruitment.

**TABLE 1** Characteristics of substance-using mothers and nonsubstance-using mothers

| | Substance-using mothers ($n = 29$) | Nonsubstance-using mothers ($n = 29$) |
|---|---|---|
| Maternal age (in years) | 28.03 (5.72) | 29.07 (6.61) |
| Maternal race/ethnicity | | |
| African American | 7 | 7 |
| European American | 18 | 18 |
| Hispanic/Latina | 4 | 4 |
| Education (in years) | 12.11 (2.48) | 13.28 (2.67) |
| Did not report | 1 | 0 |
| Marital status* | | |
| Single | 23 | 14 |
| Married | 2 | 13 |
| Divorced | 1 | 1 |
| Widowed | 0 | 1 |
| Separated | 1 | 0 |
| Did not report | 2 | 0 |
| Parity | | |
| Primiparous | 11 | 11 |
| Multiparous | 18 | 18 |
| Infant age (in weeks) | 7.17 (8.34) | 9.22 (4.91) |

*$p = .01$

## 2.2 | Apparatus and stimuli

Visual and auditory stimuli were presented to participants in a sound-attenuated room with low ambient light. Auditory and visual stimuli were presented using a Pentium IV computer and 51 cm color monitor (75 Hz, 1024 × 768 resolution) using E-Prime 1.2 software (Schneider, Eschman, & Zuccolotto, 2002). Continuous EEG was recorded using Net Station 4.2.1 with a 250 Hz sampling rate and high impedance amplifiers (0.1 Hz high pass, 100 Hz low pass). A 128 Ag/AgCl electrode net (Electrical Geodesics, Inc., Eugene, OR) was soaked in a warm KCl (i.e., potassium chloride) solution, and net electrodes were spaced evenly and symmetrically on each participant's head to cover the scalp according to manufacturer specifications (i.e., from nasion to inion, and from the left ear to the right ear). A Cz electrode was used for reference during EEG recording, and electrode impedances were kept below 40 kΩ.

Infant face stimuli included 21 color photographs of six infants (126 total images) that were unfamiliar to the participants. Infants pictured in the photographs were between 5 and 10 months of age (Strathearn & McClure, 2002). Each stimulus photograph showed an infant that was demonstrating a happy, sad, or neutral facial expression (previously validated for emotionality; Landi et al., 2011). Infant faces were presented on a black background and were on average 7.63° × 8.07° (9.32 cm × 9.8 8 cm) in size. Facial stimuli were balanced for ethnicity (Black and White) and gender (male and female). Viewing distance was approximately 70 cm.

Infant cry stimuli included 2-s audio clips of unfamiliar infants (aged 27–32 days) crying. Four different segments were used in total, composed of cries from two infants that were determined to be high-distress or low-distress (previously validated for distress level; Landi et al., 2011), resulting in both a high- and low-distress cry sample from each infant. Two examples for each distress level were used in order to avoid measuring differences associated with the particular properties of any single cry. These segments were selected from longer recordings used in previous research (see Gustafson & Green, 1989). Cries were recorded in the infants' home prior to feeding; no other additional external stimulation was utilized. In addition to infant cries, participants also heard a neutral stimulus (i.e., a 220-hz pure tone). Overall, all participants demonstrated unexpected neural responses to the pure tone, suggesting increased attentional allocation likely due to participants being surprised or confused at being presented with a sound that was not an infant cry, and exerting effort to understand the nature of the sound. Given that substance-using and nonsubstance-using mothers did not differ in their responses to the pure tone, pure tone data were not included in analyses of mothers' neural responses to infant cries.

## 2.3 | Procedure

Trials consisted of a centrally presented fixation cross, followed by stimulus presentation (face or cry/tone), and then a blank screen. The intertrial interval, which was jittered randomly and varied during both the fixation cross and blank screen, ranged between 1,400 and 2,000 ms to avoid possible expectancy effects related to stimulus onset. Face stimuli were presented for 500 ms, and auditory stimuli were presented for 2,000 ms. In the visual condition, there were 42 trials representing each of the happy, sad, and neutral faces. In the auditory condition, there were 42 trials for high-distress cries, 44 trials for low-distress cries, and 40 trials for the neutral tone. The experiment consisted of seven blocks of 42 trials, with each block containing visual trials (infant face presentations), auditory trials (infant cry or neutral tone presentations), and catch trials (see below for description) that were quasi-randomly presented, resulting in a total of 294 trials. A total of 252 experimental trials were used in the current study (catch trials were excluded from analyses). This order of presentation was uniform across participants. The overall procedure took approximately 30 min to complete.

Across the course of the experiment, a one-back memory task was administered to ensure that participants maintained attention to the stimuli being presented. These catch trials composed 14% of all trials. During the catch trials, a question mark replaced the fixation cross to indicate that a behavioral response was required. Participants were tasked with indicating whether the proceeding stimulus was the same or different than the one prior. There were a total of 42 catch trials, and the ratio of same and different catch trials was 50/50. Mean accuracy on this task was 92% ($SD = 6\%$) for faces and 93% ($SD = 9\%$) for cries, and there were no performance differences between substance-using mothers and nonsubstance-using mothers, $ts < 1, ps > .53$. These experimental trials were preceded by eight practice trials to familiarize the participant with the task. The catch trials were not included in the ERP analyses.

## 2.4 | Analysis

Net Station 4.5 was used to pre-process EEG data, which were first digitally filtered (30 Hz low-pass filter). Data were then segmented into 1-s epochs (100 ms pre- and 900 ms post-stimulus onset). Net Station artifact detection was set to 200 μV for bad channels, 150 μV for eye blinks, and 150 μV for eye movements. Channels with artifacts in more than 40% of trials were replaced through spline interpolation. Following artifact detection, EEG data were re-referenced to the average reference of all electrodes and baseline corrected to the 100 ms interval pre-stimulus onset. Last, the EEG data were averaged across stimulus conditions for each participant. Ocular Artifact Removal (OAR; Gratton, Coles, & Donchin, 1983), using a blink slope threshold of 14 μV/ms, was applied where there were fewer than 21 blink and other artifact-free trials per condition in the averaged file without using OAR. OAR was applied to data from 41 participants (70.69%). At completion of preprocessing, there were on average 35.09 trials per condition across all participants ($SD = 4.57$ trials), with no group difference in trial numbers ($t < 1, p > .93$).

For the analysis of face-processing data, N170 ERPs were assessed and averaged at six electrode sites over the left (58, 59, 64, 65, 69, and 70) and right (90, 91, 92, 95, 96, and 97) posterior scalp sites, which overlap with 10/20 electrode sites in high-dense-array EEG N170 studies (Bentin et al., 1996; McPartland, Dawson, Webb, Panagiotides, & Carger, 2004; Noll, Mayes, & Rutherford, 2012). For the analysis of auditory-processing data, N100 ERPs were assessed and averaged at 16 central electrode sites (CZ, 6, 7, 13, 31, 32, 38, 54, 55, 62, 80, 81, 88, 106, 107, and 113). These electrode sites were based on visual inspection of the grand averaged data and existing literature on the N100 in cry perception (Maupin, Rutherford, Landi, Potenza, & Mayes, 2019; Purhonen, Kilpeläinen-Lees et al., 2001; Purhonen, Valkonen-Korhonen et al., 2001). For the analysis of attentional allocation to both infant cries and faces, P300 ERPs were assessed at six electrode sites that clustered around Pz (54, 61, 62, 68, 79, and 80), consistent with prior research (Bornstein, Arterberry, & Mash, 2013; Grasso, Moser, Dozier, & Simons, 2009; Maupin et al., 2019; Proverbio et al., 2006; Rutherford et al., 2017a). Data analysis was conducted separately for each component on amplitude-to-peak and latency-to-peak measures. Effect sizes are presented as partial eta squared ($\eta_p^2$), where .01 represents a small effect size, .06 a medium effect size, and .14 a large effect size (Cohen, 1988). Cohen's $d$ is also used to present effect sizes of $t$-tests, where .20 represents a small effect size, .50 a medium effect size, and .80 a large effect size (Cohen, 1988). Greenhouse–Geisser corrections were applied when necessary.

# 3 | RESULTS

## 3.1 | Maternal responses to infant faces

### 3.1.1 | N170 analysis

Grand averaged data for infant faces averaged across left and right hemisphere electrodes for the N170 as a function of substance use status are presented in Figure 1. Two participants (one substance-using and one nonsubstance-using) were removed as outliers for N170 amplitude analyses. A repeated-measures analysis of variance (ANOVA) specifying infant facial expression (happy, sad, and neutral), hemisphere (left and right), and participant substance use status (substance-using and nonsubstance-using) was conducted to examine mothers' N170 responses to infant faces. There was no main effect of facial expression, hemisphere, or substance use status on N170 amplitude, nor were there interaction effects between facial expression and substance use status; facial expression and hemisphere; hemisphere and substance use

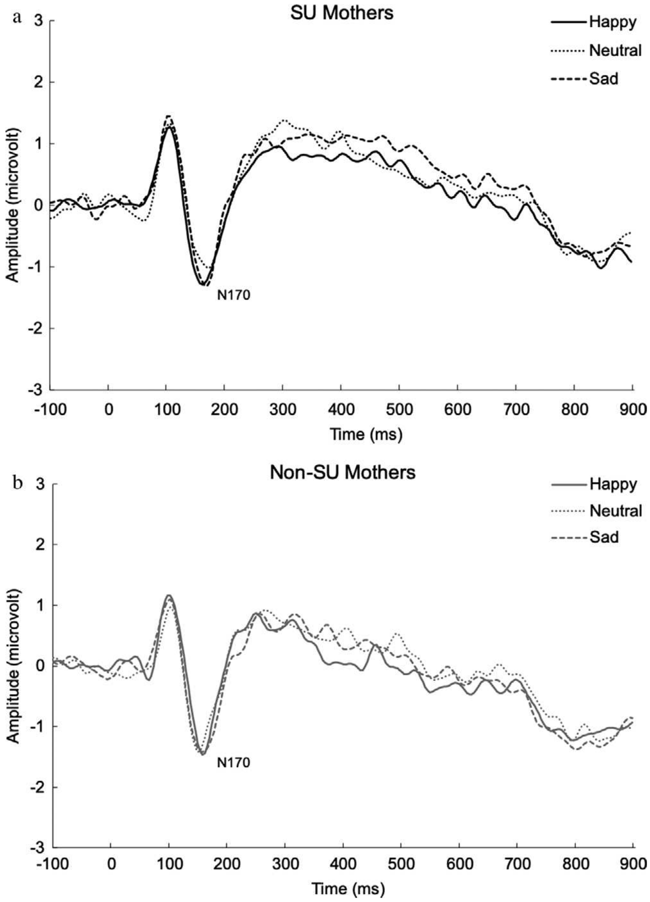


**FIGURE 1** Grand averaged ERP waveforms representing the N170 response to infant faces in substance-using and nonsubstance-using mothers. Data are averaged across hemispheres. Abbreviation: SU, substance-using

status; or facial expression, hemisphere, and substance use status on N170 amplitude ($F$s $< 2.25$, $p$s $> .12$).

With respect to N170 latency, there was no main effect of facial expression, hemisphere, or substance use status, nor was there an interaction effect between facial expression, hemisphere, and substance use status ($F$s $< 1.65$, $p$s $> .20$). However, there was an interaction between facial expression and substance use status on N170 latency, $F(2,96) = 3.49$, $p = .04$, $\eta_p^2 = .06$. This interaction appeared related to a slower N170 latency in response to neutral faces compared to sad faces in nonsubstance-using mothers, $t(28) = -2.14$, $p = .04$, $d = .27$. Substance-using mothers, in contrast, did not show statistically significant differences in N170 latency in response to varying facial expressions ($t$s $< 1.30$, $p$s $> .21$). Contrary to expectations, between-subjects $t$-tests revealed that substance-using and nonsubstance-using mothers did not differ statistically in their N170 latency for happy, neutral, or sad faces ($t$s $< 1.57$, $p$s $> .12$).

There was also an interaction between hemisphere and substance use status on N170 latency, $F(1,56) = 4.65$, $p = .04$, $\eta_p^2 = .08$. Following post hoc analyses, there was no clear differentiation in terms of hemispheric processing for substance-using mothers ($t < 1.00$, $p > .33$) and nonsubstance-using mothers ($t < -1.95$, $p > .06$) for N170 latency analysis. Further, between-subjects $t$-tests revealed that substance-using and nonsubstance-using mothers did not show differences between their N170 latencies in the right hemisphere ($t < .35$, $p > .73$) or the left hemisphere ($t < 1.53$, $p > .13$).

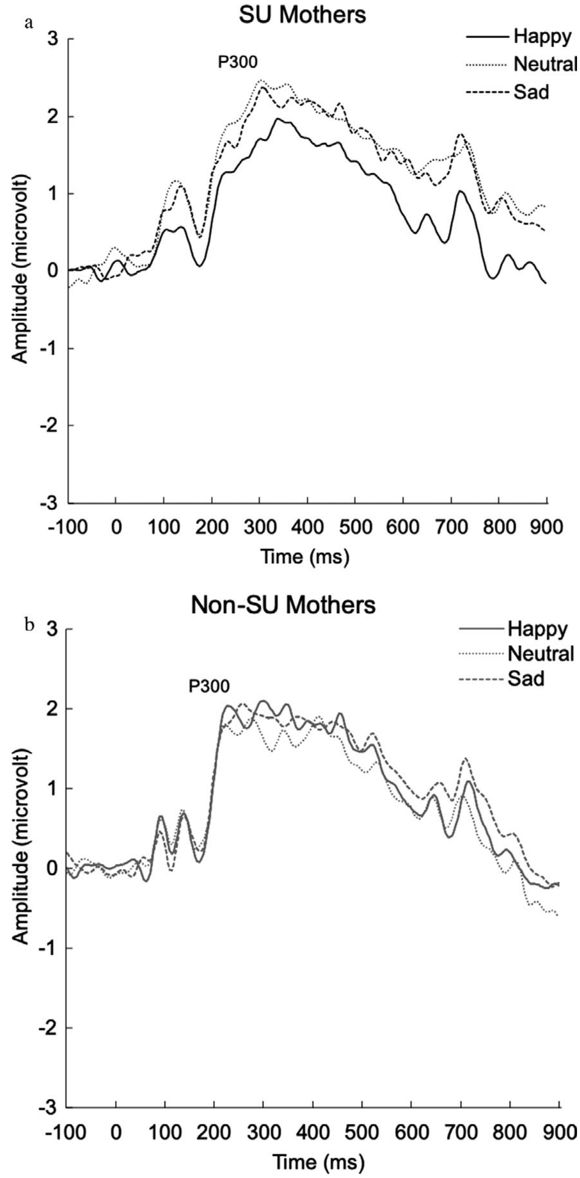


**FIGURE 2** Grand averaged ERP waveforms representing the P300 response to infant faces in substance-using and nonsubstance-using mothers. Abbreviation: SU, substance-using

### 3.1.2 | P300 analysis

Grand averaged data for infant faces for the P300 as a function of substance use status are presented in Figure 2. A repeated-measures ANOVA specifying infant facial expression (happy, sad, and neutral) and participant substance use status (substance-using and nonsubstance-using) was

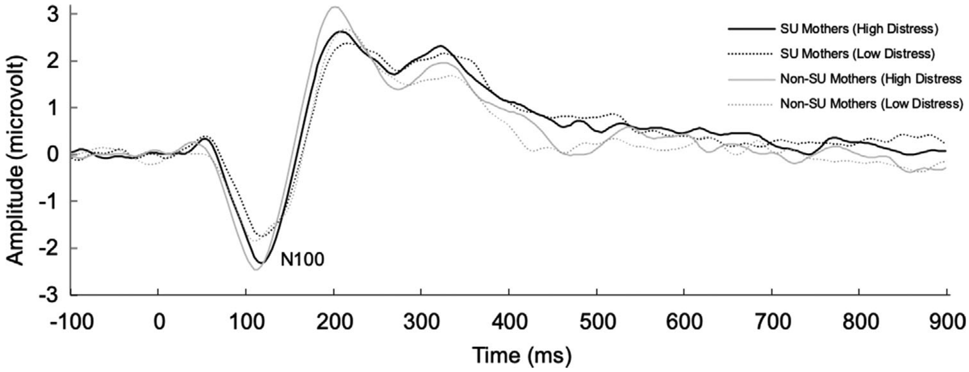


**FIGURE 3** Grand averaged ERP waveforms representing the N100 response to infant cries in substance-using and nonsubstance-using mothers. Abbreviation: SU, substance-using

conducted to examine mothers' P300 responses to infant faces. With respect to P300 amplitude, there were no main effects of facial expression or substance use status ($F$s < 1.37, $p$s > .26). However, there was a marginal interaction between facial expression and substance use status on P300 amplitude that approached statistical significance, $F(2,56) = 2.87$, $p = .06$, $\eta_p^2 = .05$. Nevertheless, given our a priori hypotheses (i.e., that substance-using mothers would demonstrate larger P300 responses to neutral infant faces) motivating this interaction, we employed post hoc $t$-tests to further understand this finding. Post hoc $t$-tests revealed that substance-using mothers showed a greater P300 amplitude in response to neutral faces compared to happy faces, $t(28) = -2.29$, $p = .03$, $d = .48$. In contrast, nonsubstance-using mothers showed no differences in their P300 responses across emotional expressions ($t$s < 1.00, $p$s > .26). Between-subjects $t$-tests indicated that substance-using and nonsubstance-using mothers did not differ in their P300 responses to happy, sad, or neutral faces ($t$s < 1.52, $p$s > .13).

## 3.2 | Maternal responses to infant cries

### 3.2.1 | N100 analysis

Grand averaged data averaged across the central electrode sites for infant cries for the N100 as a function of substance use status are presented in Figure 3. A repeated-measures ANOVA specifying infant cry type (high-distress and low-distress) and participant substance use status (substance-using and nonsubstance-using) was conducted to examine mothers' N100 responses to infant cries. With respect to N100 amplitude, there was a main effect of cry type, $F(1,56) = 15.58$, $p < .001$, $\eta_p^2 = .22$. Specifically, regardless of substance use status, mothers showed larger N100 responses to high-distress ($M = -3.84$, $SD = 2.05$) as compared to low-distress ($M = -3.36$, $SD = 1.79$) infant cries. In contrast, there was no main effect of substance use status on N100 amplitude, nor was there an interaction between cry type and substance use status on N100 amplitude ($F$s < .52, $p$s > .48).

With respect to N100 latency, there was a main effect for cry type, $F(1,56) = 13.25$, $p = .001$, $\eta_p{}^2 = .19$. Overall, regardless of substance use status, mothers were faster to respond to high-distress ($M = 113.83$, $SD = 12.17$) as compared to low-distress ($M = 19.39$, $SD = 16.34$) cries. There was also a main effect for substance use status on N100 latency, $F(1,56) = 4.77$, $p = .03$, $\eta_p{}^2 = .08$. Specifically, substance-using mothers were slower to respond to infant cries (irrespective of distress level) compared to nonsubstance-using mothers. There was no interaction between cry type and substance use status on N100 latency ($F < .83$, $p > .37$).

### 3.2.2 | P300 analysis

Grand averaged data for infant cries for the P300 as a function of substance use status are presented in Figure 4. A repeated-measures ANOVA specifying cry type (high-distress and low-distress) and substance use status (substance-using and nonsubstance-using) was conducted to examine mothers' P300 responses to infant cries. With respect to P300 amplitude, there were no main effects of cry type or substance use status on P300 amplitude ($F$s < .60, $p$s > .44). However, there was an interaction between cry type and substance use status, $F(1, 56) = 4.30$, $p = .04$, $\eta_p{}^2 = .07$. In particular, $t$-tests revealed that although substance-using mothers did not differentiate between different cry types ($t < -1.01$, $p > .32$), nonsubstance-using mothers' P300 responses were marginally greater for high-distress, relative to low-distress, cries, $t(28) = 1.89$, $p = .07$, $d = .28$.

## 4 | DISCUSSION

In this study, we utilized ERP methods to investigate whether maternal substance use status was related to the strength and timing of mothers' neural responses to infant cues. Such information has implications for parenting and infant attachment, given that effective caregiving behavior is characterized by the speed and appropriateness of the caregivers' response that

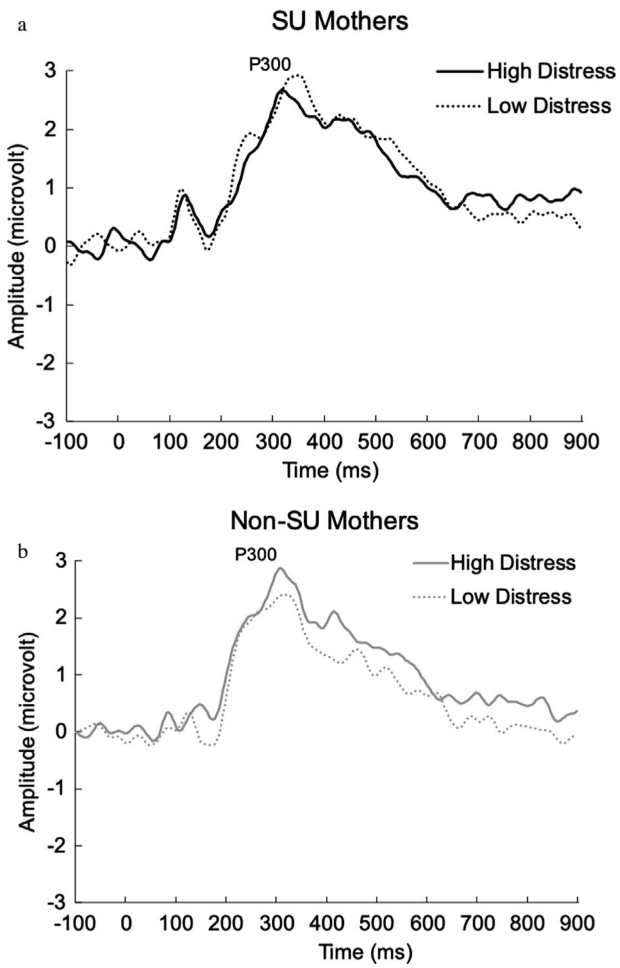


**FIGURE 4** Grand averaged ERP waveforms representing the P300 response to infant cries in substance-using and nonsubstance-using mothers. Abbreviation: SU, substance-using

is elicited by the valence of the infant's emotion and the degree of their distress.

Our findings suggest that substance use status is related to specific aspects of mothers' neural responses to infant faces and cries. In general, data suggest that at a neural level substance-using mothers, relative to nonsubstance-using mothers did not differentiate facial affect at an early encoding stage (N170 latency), were slower to encode and orient to infant cries (N100 latency), showed heightened attentional responses to neutral faces (P300 amplitude), and failed to show an adaptive pattern of attentional allocation to high-distress versus low-distress cries (P300 amplitude). Together, these differences in neural responses may be related to the caregiving differences reported in mothers who are using or in recovery from using substances.

First, we found a significant interaction between facial expression and substance use status when examining the N170. Nonsubstance-using mothers exhibited a delayed N170 latency for sad infant faces relative to neutral infant faces (see Figure 1), which mimics previous findings that individuals generally show slower latency (and greater amplitude) in N170 responses to sad infant faces compared to happy infant faces (Colasante et al., 2017). In other words, nonsubstance-using mothers are showing differential responses across facial expressions, with faster structural encoding of happy and neutral faces. Contrary to expectations, substance-using mothers did not show statistically significant differences in their N170 latencies as a function of facial expression. Our data therefore suggest that substance-using mothers may not be differentiating between infant emotions at a neural level of structural encoding of faces, which could possibly translate to less sensitive responses to infants based on their expressed emotions. More research is therefore needed in this area. In terms of N170 amplitude, there were no differences between substance-using and nonsubstance-using mothers in our study, suggesting that it is the speed with which substance-using mothers structurally encode infant faces that differs from nonsubstance-using mothers, rather than the strength of their initial neural response. The N170 amplitude results (but not latency results) found in our sample of substance-using mothers replicated those found previously in tobacco-smoking mothers (Rutherford et al., 2017a).

Next, we hypothesized that there would be an interaction between substance use status and infant emotional expression when measuring the P300, wherein substance-using mothers would demonstrate a greater P300 response to neutral infant faces. Although tests of this interaction effect were marginally significant, representing a limitation of the current study, post hoc *t*-tests of simple effects yielded significant results. Specifically, substance-using mothers showed significantly greater P300 responses to neutral faces compared to happy faces (see Figure 2). These results are similar to those found previously in a sample of tobacco-smoking mothers in which the P300 amplitude was greatest when elicited by neutral faces relative to happy and sad faces (Rutherford et al., 2017a). The findings suggest that substance-using mothers may be allocating more attention to infant cues that are neutral rather than those that are either positively or negatively valenced. Given previous findings that healthy adults show larger P300 responses to sad infant faces (Proverbio et al., 2006), we were surprised that the nonsubstance-using mothers in our study did not show this differentiated P300 responses based on infant facial expression, whereas substance-using mothers did. However, our finding that substance-using mothers showed the largest P300 in response to neutral faces was notable given previous findings that healthy adults showed attenuated P300 responses to infant faces of low emotional intensity (i.e., neutral faces; Proverbio et al., 2006). Our results also complement previous fMRI findings suggesting that happy faces are less salient for substance-using mothers, and that substance-using mothers exhibit a dampened neural reward response to positive infant cues (Landi et al., 2011). Additionally, higher amplitudes in late ERP components (i.e., the late positive potential or LPP) in response to neutral infant faces were shown to be associated with maternal anxiety and thought to be related to the ambiguity of the neutral stimuli (Malak, Crowley, Mayes, & Rutherford, 2015). It is therefore possible that substance-using mothers are employing increased attentional resources in response to neutral cues due to anxiety, or are exerting more effort to understand or determine the valence of neutral faces. This is in contrast to maternal depression that is associated with attenuated P300 responses to sad infant faces but not neutral or happy faces (Rutherford, Graber, & Mayes, 2016), suggesting that substance use may have a unique impact on neural responses to infant cues relative to other forms of psychopathology or tobacco addiction.

Substance-using mothers also demonstrated a significantly delayed N100 response to all infant cries, suggesting that they may process the sound of an infant cry less efficiently than nonsubstance-using mothers (see Figure 3). Our results provide objective neurological evidence that may underlie the decreased behavioral sensitivity to infants and impaired caregiving behaviors demonstrated by substance-using mothers reported previously (Mayes & Truman, 2002; Suchman, DeCoste, Castiglioni, Legow, & Mayes, 2008; Suchman, DeCoste, Leigh, & Borelli, 2010). Given that effective caregiving behavior is characterized by the match between infants' affective cues and the speed and accuracy of caregivers' responses, our results have implications regarding substance-using mothers' ability to respond quickly and sensitively to their infants' cues. Maternal responses that have been compromised by substance use have been shown to impact attachment relationships between infants/children and substance-using mothers (Mirick & Steenrod, 2016; Quinlivan & Evans, 2005). For example, when faced with compromised maternal responsiveness illustrated here, an infant may learn that the mother is slow or inaccurate in recognizing their cues and may then respond in turn by demonstrating insecure behaviors (i.e., avoidance and anxiety) as a result.

Finally, an interaction between substance use status and cry distress level was observed for P300 amplitude that appeared to be related to substance-using mothers not demonstrating differences in the strengths of their P300 responses to infant cries, whereas nonsubstance-using mothers did (see Figure 4). In other words, substance-using mothers did not differentiate between high-distress and low-distress cries; instead, they exhibited equally strong responses to cries of all types and showed heightened responses to infant cries even when distress was low. Nonsubstance-using mothers, on the other hand, appeared to differentiate more robustly between high-distress and low-distress cries, permitting greater allocation of attention to high-distress cries (which may be related to an infant's physical pain and/or threat of harm) compared to low-distress cries (which may be related to an infant's minor discomfort or upset). Although tests of these interaction effects were statistically significant, post hoc *t*-tests of simple effects were marginally significant and therefore should be interpreted with caution and used to guide future research questions. Nonetheless, we propose it is possible that nonsubstance-using mothers may be demonstrating an adaptive pattern of allocating their attention (as indexed by the P300) based on the amount of distress an infant is showing (thus prompting a sensitive caregiving response), whereas substance-using mothers may be interpreting all cries as equally distressing at the neural level. Our results seem to be driven by the differences in the way mothers respond to low-distress cries based on substance use status. These results are comparable to previous fMRI findings that substance-using mothers and nonsubstance-using mothers differed in terms of the activation of reward circuits in response to low-distress cries but not high-distress cries (Landi et al., 2011). Future research should attempt to replicate these results in order to confirm or disconfirm whether substance-using mothers may be experiencing similar levels of subjective internal stress or activation in response to both high- and low-distress cries, whereas nonsubstance-using mothers may be experiencing levels of internal distress that are proportionate to the amount of distress being indicated by the infant.

## 4.1 | Implications

Given that substance-using mothers did not evidence N170 latency modulation by facial affect and had delayed N100 responses to infant cries compared to nonsubstance-using mothers, and given that at later attentional processing stages, substance-using mothers had stronger P300 responses to neutral infant faces and showed an undifferentiated pattern of P300 responses to low-distress and high-distress cries, our findings provide insight into the neural mechanisms that may underlie links between addiction and impairments in caregiving. The findings have implications for caregiving behaviors and attachment formation in particular given that infants may learn to adapt their cues contingent upon the responses of their mothers. Specifically, an infant within a secure mother-child dyad should learn to "cue" the parent that they have a physical or emotional need to be met, whereas an infant who has learned that the mother is slow or inaccurate in processing or responding to his/her needs may learn to "miscue" or hide a need in order to maintain connection and decrease the likelihood of further parental dysregulation, resulting in an insecure attachment relationship (Hoffman, Marvin, Cooper, & Powell, 2006). Although some research suggests that maternal neural activation (as measured by fMRI) is related to infant attachment security (Laurent & Ablow, 2012), additional research is needed to determine whether maternal ERP components are related to infant attachment, generally, as well as specifically in substance-using populations. Nonetheless, ERP research methodology may be particularly helpful in the study of parent–child relationships given that it allows researchers to examine different stages of neural processing and make interpretations regarding maternal perception, attention, and cognition surrounding infant cues (Maupin et al., 2015). Our findings may therefore serve to inform interventions with substance-using mothers aimed at improving parent–child outcomes.

Traditionally, many parenting interventions studied in substance-using families have adopted curriculum-based cognitive-behavioral approaches and skills training techniques focused on teaching parents strategies for improving child behavior (Bröning et al., 2012; Catalano, Gainey, Fleming, Haggerty, & Johnson, 1999; Haggerty, Skinner, Fleming, Gainey, & Catalano, 2008; Kumpfer, Alvarado, & Whiteside, 2003). Unfortunately, such programs have not typically demonstrated long-term improvements in child development or the quality of the mother–child relationship, suggesting the importance of implementing an alternative treatment approach with this population (Suchman, Pajulo, DeCoste, & Mayes, 2006). Instead, parenting interventions that focus on the emotional quality of the parent–child relationship itself rather than on teaching specific parenting behaviors (e.g., limit-setting, problem-solving, communication, and coping skills) have shown promise in improving attachment security, mother–child interactional quality, and child development in general high-risk populations (e.g., "Attachment and Biobehavioral Catch-up"; Dozier, Meade, & Bernard, 2014; "Circle of Security"; Powell, Cooper, Hoffman, & Marvin, 2014). Given substance-using mothers' unique behavioral presentation (Eiden, Stevens, Schuetze, & Dombkowski, 2006; Molitor, Mayes, & Ward, 2003), neural profiles (Kim et al., 2017; Landi et al., 2011), and typically high trauma load (Covington, 2008; Gil-Rivas, Fiorentine, & Anglin, 1996; Marcenko, Kemp, & Larson, 2000), researchers and clinicians alike have noted the need for specialized parenting interventions designed with this population in mind.

*Mothering from the Inside Out* (MIO), for example, was developed as one such evidence-based parenting psychotherapy program designed specifically for substance-using mothers (Suchman et al., 2008; Suchman, DeCoste, Ordway, & Bers, 2013). MIO adopts a mentalization-based approach (Allen, Fonagy, & Bateman, 2008) that considers substance-using mothers' psychological and relational vulnerabilities rather than teaching skills or delivering a curriculum. Overall, this approach involves facilitating the mother's ability to reflect upon the mental states (i.e., thoughts, emotions, and intentions) underlying her own and her child's behavior. Mentalization-based parenting interventions such as MIO are particularly warranted in light of the results of the current study as well as other neuroscientific findings suggesting that substance-using mothers process and experience infant cues differently on a neural level compared to nonsubstance-using mothers (Kim et al., 2017; Landi et al., 2011).

Using this framework, mentalization-based parenting intervention may involve helping a mother reflect on which of her infant's cues she notices most quickly or to which infant cues she pays most attention. In service of helping the mother improve her ability to mentalize for herself, clinical work may also focus on encouraging the mother to reflect on how her mental states, stress levels, and previous experiences within relationships (including trauma) impact her perception of infant cues. With regard to facilitating the mother's ability to mentalize for her child, the clinical focus may shift to helping the mother consider how her mental states and corresponding behavioral responses impact her infant's perception of her, their relationship, and the subsequent behaviors her child exhibits within their relationship. Carefully timed, attachment-informed developmental guidance is also integral to building the mother's capacity to mentalize about the intentions, thoughts, and emotions underlying her infant's behavioral cues, as well as what her infant's cries or facial expressions may possibly be communicating. Throughout treatment, the clinician is encouraged to model openness and inquisitiveness to the many possible mental states that could be present in either the mother or child with the goal of increasing the mother's flexibility and curiosity about her own and her child's experiences.

Not only might neuroscientific research inform mentalization-based parenting interventions for substance-using mothers, but it also may be possible that helping substance-using mothers become more regulated through the process of mentalization could improve their ability to notice their infants' cues more quickly, differentiate among cues, and pay appropriate attention to cues at the neural level in ways that could translate to maternal behavior and enhance the mother–child bond. Interestingly, mentalization and reflective functioning have indeed been shown to correlate with mothers' neural responses to infant cues, with greater P300 and LPP responses to infant cues being associated with self-reported reflective functioning (Rutherford et al., 2017b, 2018). Thus, it may be worthwhile to examine how mentalization-based interventions may impact substance-using mothers' neural responses to infant cues.

## 4.2 | Limitations

It is important to consider the findings of this study in light of its limitations and directions for future research. First, our sample size was limited due to challenges in recruiting substance-using mothers for participation in research. Our results should therefore be interpreted with caution and highlight the importance of examining similar neural mechanisms in a larger sample of substance-using mothers in order to confirm or disconfirm our findings. Next, our measures of substance use status were limited to mothers' self-reported history of using substances or participating in substance-use treatment, and we did not know how recently mothers had used substances before the laboratory visit or for how long they had been in treatment. There was also a high degree of heterogeneity of substances that were reportedly used by mothers in our sample. Although polysubstance use is characteristic of current behavioral patterns of substance use, we do acknowledge that different substances may result in different neurochemical and behavioral consequences. Our results, however, add to the literature given that the findings signify how an addictive process may impact neural responses in mothers. Future research should examine whether varying substances differentially impact mothers' neural responses to infant cues. Additionally, future research should study differences in neural responses exhibited by mothers who are in recovery versus those who, for example, are on opioid replacement therapy, and those who are actively using substances.

Although stimuli were presented quasi-randomly, the order of the stimuli was uniform across participants and therefore future research should fully randomize stimulus presentation across participants. Additionally, although this is one of the first ERP studies to examine how maternal substance use may influence the strength and timing of mothers' neural response to infant cues, other factors that have been shown to impact maternal responsivity were not included and may further inform our understanding of how substance-using mothers may differ in their neural responses to infants (and how this may be manifested behaviorally). For example, our stimuli included only infant faces and cries that were unfamiliar to participants. Therefore, future studies may wish to examine how substance use may affect mothers' neural responses to their own infants' signals of distress. Given previous research indicating that mothers exhibit stronger sympathetic nervous system responses to their own infant's cries, and that they are able to identify the type of cry more accurately in their own infant than in unfamiliar infants (Wisenfeld, Malatesta, & DeLoach, 1981), it would be worthwhile to examine whether the same holds true for substance-using mothers. In addition, future research should study whether familiarity alters substance-using mothers' strength and latency of neural processing or allocation of attention, or whether substance-using mothers respond similarly to infants regardless of familiarity. Finally, further research is needed to determine whether differences in substance-using mothers' neural responses to infant cues translate to actual caregiving (i.e., maternal sensitivity, bonding, and reflective functioning) as measured by behavioral observation, interview responses, and self-report measures.

## 5 | CONCLUSIONS

The current study examined ERP responses to infant affective cues (i.e., faces and cries) in both substance-using and nonsubstance-using mothers. At initial stimulus-processing stages, we found that substance-using mothers did not evidence N170 latency modulation by facial affect and had delayed N100 responses to infant cries compared to nonsubstance-using mothers. At later attentional-processing stages, we found that substance-using mothers had stronger P300 responses to neutral infant faces, and showed a maladaptive undifferentiated pattern of P300 responses to low-distress and high-distress cries. Together, these data provide evidence to suggest that infant cues are processed differently in substance-using mothers, which may have implications for caregiving responses. Our study also supports the value of utilizing ERP methods to inform the neurobiological mechanisms that underscore how infant cue perception may be compromised in substance-using mothers. Findings also emphasize the importance of continuing to examine how the neurobiological basis of infant cue perception translate to caregiving behaviors. Finally, our study may serve to help researchers refine parenting interventions for substance-using mothers in order to facilitate their ability to quickly process and more adaptively attend to infant cues in an effort to improve parent–child relationships and overall familial mental health.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest. Dr. Potenza has consulted for and advised Rivermend Health, Opiant/Lightlake Therapeutics and Jazz Pharmaceuticals; received research support from the Mohegan Sun Casino and the National Center for Responsible Gaming; and consulted for legal and gambling entities on issues related to impulse-control disorders and addictions. The other authors report no disclosures.

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