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To cite this article: Kristen P. Morie, Jia Wu, Nicole Landi, Marc N. Potenza, Linda C. Mayes & Michael J. Crowley (2018) Feedback processing in adolescents with prenatal cocaine exposure: an electrophysiological investigation, *Developmental Neuropsychology*, 43:3, 183-197, DOI: [10.1080/87565641.2018.1439945](https://doi.org/10.1080/87565641.2018.1439945)

To link to this article: <https://doi.org/10.1080/87565641.2018.1439945>



Published online: 20 Feb 2018.



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Feedback processing in adolescents with prenatal cocaine exposure: an electrophysiological investigation

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ABSTRACT

Impaired cognitive control is a consequence of cocaine exposure. Difficulty with feedback processing may underlie this impairment. We examined neural correlates of feedback processing using event-related potentials (ERPs) in 49 prenatally cocaine-exposed (PCE) and 34 nondrug exposed (NDE) adolescents. Adolescents performed a reward-feedback task with win/no-win feedback in a chance-based task. We investigated amplitude and latency of the feedback-related negativity (FRN) and P300 ERP components and source-based estimates elicited during feedback processing. PCE adolescents had smaller P300 amplitudes for no-win feedback, and source analysis in the P300 time window revealed differences between groups localized to the dorsal anterior cingulate cortex.

Introduction

Prenatal cocaine exposure (PCE) is associated with a range of negative outcomes in children and adolescents, including poorer inhibitory control (Bridgett & Mayes, 2011), higher prevalence of mood disorders (Linares et al., 2006), increased aggression and greater risk-taking, (Bennett, Bendersky, & Lewis, 2007), and importantly, an increased susceptibility to initiation of drug use (Richardson, Larkby, Goldschmidt, & Day, 2013). Given these broad deficits in self-regulatory functioning, feedback processing, which plays a strong role in cognitive control and decision-making (Schuermann, Endrass, & Kathmann, 2012), is a good candidate process for examining the neuro-developmental effects of PCE. This process may be governed by a midbrain dopamine system that represents expectations and fluctuates dopamine release based upon outcomes that confirm or violate those expectations (Holroyd & Coles, 2002). PCE may impair the development of this feedback-learning system, underlying the behavioral outcomes seen in this population.

Neural response in feedback-learning contexts may be used to examine reward processing. The feedback-related negativity (FRN) event-related potential (ERP) is a well-documented ERP component associated with reward-based feedback learning (Hajcak, Moser, Holroyd, & Simons, 2006). Occurring reliably between 200 and 300 ms post-feedback, the FRN is larger for unexpected, typically worse, or negative outcomes, and is sensitive to both reward-magnitude (Bellebaum, Poleszki, & Daum, 2010) and reward-expectation violations (Cohen, Elger, & Ranganath, 2007), as well as risk-taking propensity (Crowley et al., 2009) and substance-use-related risk (Euser et al., 2013;

Fein & Chang, 2008). The P300 ERP response is also elicited in reward-processing and feedback-learning contexts, including gambling (Wang, Zheng, Huang, & Sun, 2015; Zhang et al., 2013), reward (Bellebaum et al., 2010; Morie, De Sanctis, & Foxe, 2014a), and decision-making (Twomey, Murphy, Kelly, & O'Connell, 2015) tasks. Whereas the FRN reflects whether outcomes are worse or better than expected (feedback valence), information about how much better or worse the outcome was than expected (feedback magnitude) more strongly affects P300. The P300 tends to be more pronounced following a larger magnitude feedback regardless of valence (Begleiter, Porjesz, Chou, & Aunon, 1983; Homberg, Grunewald, & Grunewald-Zuberbier, 1981; Sato et al., 2005; Yeung & Sanfey, 2004). However, some studies report larger P300 amplitudes for positive feedback (Bellebaum & Daum, 2008; Hajcak, Holroyd, Moser, & Simons, 2005; Hajcak, Moser, Holroyd, & Simons, 2007), while others report larger P300 amplitudes for negative feedback (Crowley et al., 2009; Frank, Woroch, & Curran, 2005).

Feedback learning has been well characterized in healthy adults (Ridderinkhof, Van Den Wildenberg, Segalowitz, & Carter, 2004) and adolescents (Reyna & Farley, 2006), where it has been established that immaturity in feedback-learning capabilities is associated with the greater risk-taking seen in adolescent populations (Fisher et al., 2011; Geier, 2013). In turn, increased risk-taking, poorer reward-processing, and poorer cognitive-control in adolescents are associated with increased use of substances later in life (Geier, 2013).

Feedback learning, as evidenced by the FRN, develops over time in adolescence, with larger amplitudes and longer latencies in younger ages (Crowley et al., 2013). Among adults, substance dependence is associated with altered feedback-learning capabilities, with impaired inhibitory and cognitive control (Franken, Van Strien, & Kuijpers, 2010; Morie, De Sanctis, Garavan, & Foxe, 2014b), poorer reevaluation of task outcome (Morie, 2016), and a reduced response to punishment (Franken, Van Strien, Franzek, & Van De Wetering, 2007). Adult substance users, as well, demonstrate impaired feedback learning (Parvaz et al., 2015) and poorer reward processing (Baker, Wood, & Holroyd, 2016), and this poorer reward processing is especially severe in recently abstinent cocaine users (Parvaz et al., 2012).

PCE is associated with risky decision-making and increased initiation of substance use over and above that seen in NCE adolescents (Minnes et al., 2014). The dopaminergic basis of feedback learning and cognitive control (Schultz, Dayan, & Montague, 1997) as well as the clear effects of PCE on D1 receptors, dopamine binding, and reward response found in preclinical work (Malanga, Riday, Carlezon, & Kosofsky, 2008; Wang, Runyan, Yadin, & Friedman, 1995), suggests the importance of determining if PCE impairs feedback learning in adolescents similar to the impaired feedback learning seen in cocaine-using adults.

It should be noted that individuals with PCE are often raised in homes that may be sources of stress, and it is important to mention factors that may affect feedback processing that that may be only tangentially related to substance use and exposure. Stress is known to affect feedback processing (Banis, Geerligs, & Lorist, 2014). In addition to this, increased trait anxiety in particular has been associated with amplitudes of the FRN (Olvet & Hajcak, 2009), and the direction and strength of the association depends upon the nature of the feedback (Gu, Huang, & Luo, 2010) as well as risk-taking context (Takacs et al., 2015). This is relevant considering the stressful environment many PCE children and adolescents experience.

Given previously discussed findings suggesting that PCE can be associated with a range of dysregulated behaviors (Fisher et al., 2011), and preclinical animal models suggesting direct impacts of PCE on reward processing (Hecht, Spear, & Spear, 1998), we hypothesized that PCE may result in an altered response to feedback. However, there is a scarcity of research that has examined ERP correlates of these capabilities in PCE adolescents. If they exist, feedback-processing deficits may indicate a preexisting vulnerability that could predispose to initiation of substance use, as impaired feedback processing could lead to a resistance to negative outcomes associated with drug use.

The goal of this work was to determine if PCE has an effect on feedback processing of rewards versus non-rewards. To do this, we investigated the reward-sensitive FRN and the subsequent P300

using a rewarded choice-feedback task in a cohort of adolescents who were exposed to cocaine prenatally (PCE), and a cohort of control adolescents with no exposure (NCE). The task was presented as a game where choices could result in either not winning anything (draw outcome) or winning money (win outcome), and the FRN and P300 responses to presentation of the draw and win feedback were analyzed. We performed between-group analyses on the amplitude and latency of our components of interest as well as examining source analysis of these components. We also investigated source-analysis waveforms. We hypothesized that PCE adolescents would show poorer feedback-monitoring, evidenced by smaller FRN and P300 amplitudes and shorter latencies than comparison subjects who were nondrug exposed (NDE) in utero. In addition, we conducted exploratory analyses of the sources of these waveforms between PCE and NDE adolescents.

Methods

Participants

Participants were recruited from a larger cohort of 369 individuals who were enrolled in a longitudinal, 17-year study examining the long-term effects of PCE on physical, cognitive, social, and emotional development. The total sample consisted of three groups. All children in the PCE group were exposed to cocaine *in utero*. Children and their mothers who were exposed to drugs other than cocaine (primarily alcohol, tobacco, and/or marijuana) were also enrolled in the study. Nondrug using mothers and their NDE children were enrolled to serve as a control group. The sample was recruited at birth over a 5-year period and children and their parents have been seen biannually. Families were originally recruited when they presented for prenatal care at the Women's Center of the Yale-New Haven Hospital or, in the case of no prenatal care, when they were admitted to the postpartum ward. Maternal cocaine use was determined based on maternal self-report, on urine toxicology during pregnancy or following delivery, and for some individuals, on meconium toxicology in the infant. The larger sample from which the children for this study were drawn consisted of 81% African-American, 6.5% Hispanic, and 12.5% Caucasian children, all of who come from the greater New Haven area (Bridgett & Mayes, 2011; Mayes, Molfese, Key, & Hunter, 2005; Rando, Chaplin, Potenza, Mayes, & Sinha, 2013; Yip et al., 2014), and reflects the demographics of this location. From this larger sample, we recruited 49 adolescents (average age 17.6 years, $SD = 2.0$, 21 female/28 male) with prenatal exposure to cocaine and 34 adolescents (average age 16.8 years, $SD = 1.8$, 22 female/21 male) with no such exposure, for a total of 83 participants. Of this subsample, 77.1% were African-American, 4.3% were Hispanic, and 17% were Caucasian, with 1 participant reporting as "other." Participants from the subsample did not differ significantly from the larger sample on race ($\epsilon = 2.01$, $p = .15$), gender ($\epsilon = 46$, $p = .49$), or SES ($\epsilon = 66$, $p = .41$). Participants from all three groups in the longitudinal study visit the lab twice yearly for check-ins. They perform the Teen ASI (Kaminer, Bukstein, & Tarter, 1991) and provide urine, breathalyzer, and CO2 monitor measures. Upon their yearly visits, if they qualified for the study, expressed interest in participating and willingness to perform EEG procedures, they were recruited for this study. Participants were between the ages of 15–19 while recruitment for this study was on-going. This specific cohort of 83 individuals was also examined previously in a study concerning language processing (Landi, Crowley, Wu, Bailey, & Mayes, 2012). Among the mothers of the PCE individuals in this specific cohort, 63% reported some marijuana use, 63% reported some alcohol use, and 20.4% reported nicotine use during gestation. Simultaneous use of multiple substances is very common in substance users. Since not every PCE adolescent was exposed to other substances, and every mother in the PCE group indicated cocaine use, for the purposes of this study, we focused upon cocaine exposure. Among NCE individuals, mothers reported using no substance use during pregnancy, although three of the mothers reported some tobacco use in their lifetime.

There were no differences between groups in gender distribution ($\epsilon = .63$, $p = .51$), socioeconomic status as indicated by the mother's years of education ($\epsilon = .40$, $p = .53$), or ethnicity/race ($\epsilon = 2.6$,

$p = .095$), though there was a trend toward a difference in age ($F_{1,82} = 3.8, p = .052$), where PCE adolescents were an average of 17.6 ($SD = 2.0$) years and NCE adolescents were an average of 16.8 ($SD = 1.8$) years. Adolescent participants also reported their own substance use histories at the time of recruitment. Initiation status for a substance was determined based upon participant’s self-report of use in the past 3 months and how often they reported using. It was apparent that PCE participants had higher rates of initiation of substances, including alcohol ($\epsilon_{1,82} = 11.09, p < .003$) and marijuana ($\epsilon_{1,82} = 5.04, p < .03$). These demographics are illustrated in Table 1.

Task

The task was presented to participants as a game called, “Money Maker.” This task has been used before by our group to investigate FRN responses in children of different ages (Crowley et al., 2013). The task is illustrated in Figure 1. Stimuli were presented on a 17-inch Dell monitor. Participants were told that they would be playing a game that involved selecting among balloon icons to win money. The goal of the game was to win as much money as possible and participants were told that they would receive the money they won at the end of the game. At the beginning of each trial, participants were presented with four balloon icons of different colors (red, green, orange, blue) that

Table 1. Demographics.

	NCE (N = 34)	PCE (N = 49)	F or ϵ	p
Age	17.1 (1.9)	17.6(2.0)	1.01	0.30
Gender (M)	19(15)	21(28)	0.633	0.56
Ethnicity			1.55	0.22
African-American	23	44		
Hispanic/Latino	2	1		
Caucasian	9	3		
Other	0	1		
Substance initiation by subject (%)				
Alcohol	11(32)	34(69)	11.09	0.002
Marijuana	13(38)	31(63)	5.048	0.028
Nicotine	8(23)	16(32)	0.813	0.463
Any	18(52)	38(77)	5.5	0.031

Money Maker: Balloon Reward Task

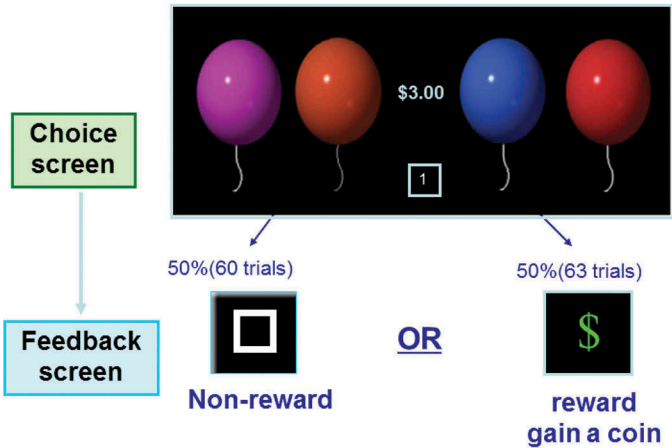


Figure 1. An illustration of the task.

randomly appeared in different spatial positions along a row centered on the screen. Participants responded with their right and left middle and index fingers on a four-button response pad. After the participant made their selection, all of the balloons disappeared, and either a green dollar sign (indicating a reward of 10 cents, a win condition), or a white square (indicating a non-reward, a draw condition) appeared. Feedback stimuli were delayed 1–1.2 sec after balloon selection and lasted 1,000 msec. After the feedback, a 1,000–1,200 msec crosshair was presented, followed by a 100 msec blank screen, and then the balloons reappeared. Participants made balloon choices at self-paced intervals. The running totals of participant earnings were displayed numerically on the screen throughout each trial, centered between the middle two balloons.

Although there were four options (balloons) on a given trial, the game was structured such that there was a probability of 50% win and 50% draw outcomes across the task. Feedback was random, meaning that there was no pattern of certain balloons predicting specific outcomes, but participants were instructed that some people may “figure out a pattern some of the time.” Participants maintained central fixation throughout each block.

There were four blocks of trials with 30 trials in each block. After each block, a clear glass coin jar appeared to reflect the cumulative winnings to that point. Realistic dime images appeared in the jar, one by one, each followed by a coin sound. Prior to beginning the game, there were three practice trials, which introduced the coin jar. A total of 120 trials (60 per condition of win or draw) were administered for the purpose of computing ERPs. Three additional trials were added such that the total winnings were \$6.30 for each participant. Participants received this payment as part of a larger compensation (\$70) for a study on language.

ERP methods and analysis

Acquisition

Participants were seated 1 m in front of the computer, and their heads measured to determine appropriate electrode net size. ERPs were acquired from a 128-channel sensor net of Ag/Cl electrodes. The nets were soaked in a potassium chloride solution for 10 min beforehand to ensure low impedance without the need for abrading the participant's scalp. Recording was performed at a sampling rate of 250 Hz using the Netstation v4.4 software and EGI high impedance amplifiers (EGI, Inc. Series 300 amplifier). All electrodes were referenced to Cz for recording and then re-referenced offline for data analysis. All impedances were determined to be under 40 kohms before recording began.

Data processing

Data were processed off-line through a 0.1 Hz first-order high-pass filter and a 30 Hz low-pass filter. For the FRN and P300 for both draw and win conditions, epochs of 900 ms, including a 100 ms pre-stimulus baseline, were analyzed. Eye channels were inspected visually and flat channels or those reflecting a great deal of noise were interpolated using surrounding channels. Automatic artifact rejection removed any segments containing extreme voltage fluctuations (threshold 200 μ V) or muscle activity association with saccades and eye blinks (threshold 150 μ V). Epochs with any eye blink or eye movement (threshold 150 μ V) were rejected. Epochs with more than 10 bad channels (40% or more segments marked bad) were rejected as well. Any bad channels were replaced by surrounding channels. Participants with more than 20% of all trials being marked bad were removed from analysis. Only one NCE participant was removed from analysis for poor data quality. Two additional PCE participants were removed for particularly noisy data upon visual inspection (many blink artifacts).

Analysis

Visual inspection of the draw and win conditions showed maximal FRN amplitude at 250 ms over fronto-central scalp locations (corresponding to electrodes 11, 20, 4, 5, 12, 10, and 19) and was thus

defined as the peak average amplitude of these electrodes in the time window between 220 and 300 ms at this location, matching the observed peak latency of this waveform. Maximal P300 amplitude was observed to begin at 300 ms and peak at 400 ms over central-parietal scalp sites (corresponding to electrodes 55, 54, 80, 62). It was thus defined as the peak average amplitude of these electrodes in the time window between 300 and 400 ms, matching the observed peak latency. Despite the younger age of participants examined in this study, these time windows were relatively consistent with previous literature on the FRN (Hajcak et al., 2006) and P300 (Sato et al., 2005) elicited during feedback tasks. An illustration of the electrode net and the electrodes used in the analyses can be seen in [Figure 2](#). For the ERP data, two repeated measures ANCOVAs were generated, one for the FRN and one for the P300, with factor of condition (win or draw) and group (NCE or PCE), for both waveform amplitude and for waveform latency. Gender, drug use initiation status, and age were included as covariates.

Source analysis

Source analysis was conducted using GeoSource software, version 1.0.1 (electrical Geodesics, Eugene, OR). The neural sources of the FRN and P300 were computed using the distributed linear inverse minimum norm approach with sLAURA constraints (Grave De Peralta Menendez, Murray, Michel, Martuzzi, & Gonzalez Andino, 2004). Dipoles served as a source location with three orthogonal orientations of 7mm voxels. This resulted in 2447 source dipole triplets. Five source regions corresponding to the FRN and P300 were selected. Source waveforms within each Brodmann Area (BA) were generated from the models. These waveforms were analyzed using mean amplitude measures within each BA. For the P300, there were two time courses investigated, as the P300 is a long, sustained waveform, and the source peak is not well-defined by the time window of 300–400 ms. The first was between 300–400 ms, which corresponded to the time window selected for the P300 amplitude, and the second time-course was between 400–600 ms, which more closely represents the source peak. The time course for the FRN was between 150–300 ms. We focused on BA 10 (anterior prefrontal cortex), BA 11 (orbitofrontal cortex), BA 24 (ventral posterior cingulate cortex), BA 25 (subgenual anterior cingulate cortex (ACC)), and BA 32 (dorsal ACC). These regions have been implicated as important in previous literature for reward and feedback processing (Amiez et al., 2013; Barch et al., 2001; Hauser et al., 2014; Sescousse, Redoute, & Dreher, 2010), and were

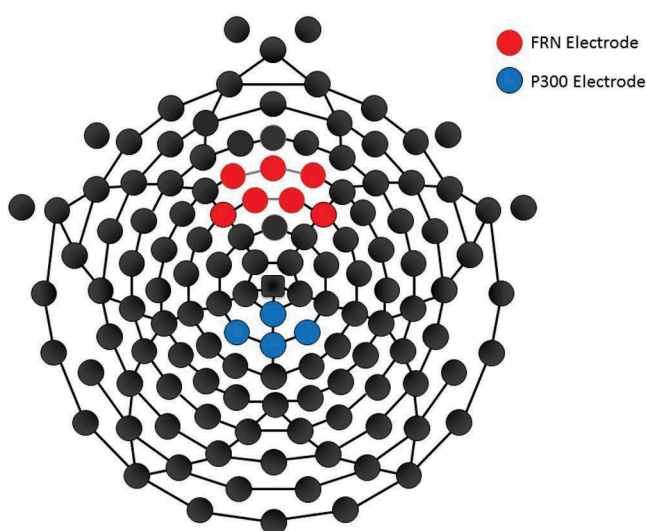


Figure 2. An illustration of the electrode net with electrodes used in analyses highlighted.

previously examined in (Crowley et al., 2013). Two 2-(Condition)-by-5-(region)-by-2-(group) repeated measure ANCOVAs for the FRN and the P300, with factors of condition (win or draw), region (BA 10, 11, 24, 25, 32), and group (PCE or NCE) were conducted. Areas were averaged across the right and left hemispheres.

Results

Amplitude analyses

FRN

The ANCOVA for the FRN revealed significance for condition (draw versus win) ($F_{1,82} = 10.12$, $p < .01$, $\eta^2 = .29$), no significance for group ($F_{1,82} = .055$, $p = .44$), and no significant interaction of condition and group ($F_{1,82} = .079$, $p = .77$). As expected, FRN values were larger for draw conditions ($M = -3.03$, $SD = 2.2$) than for win conditions ($M = -1.46$, $SD = 1.4$).

P300

The ANCOVA for the P300 (draw versus win) was significant for condition ($F_{1,82} = 8.91$, $p < .005$, $\eta^2 = .09$) and for the interaction of condition-by-group ($F_{1,82} = 4.50$, $p < .04$, $\eta^2 = .05$), though there was no main effect of group ($F_{1,82} = 1.82$, $p = .16$). P300 values were larger for win conditions ($M = 3.79$, $SD = 2.0$) than for draw conditions ($M = 3.1$, $SD = 1.6$). PCE adolescents had significantly smaller P300 amplitudes during a draw condition ($M = 2.7$, $SD = 1.6$) than NCE adolescents ($M = 3.6$, $SD = 1.8$). Values for latency and amplitude for both PCE and NCE adolescents in both win and draw conditions can be seen in Table 2, and ERP waveforms can be seen in Figure 3.

Latency analyses

FRN

The ANCOVA for the latency of the FRN revealed no significance for condition ($F_{1,82} = .19$, $p = .66$), group ($F_{1,82} = .073$, $p = .78$), or any interaction ($F_{1,82} = .75$, $p = .4$).

P300

The ANCOVA for the latency of the P300 revealed no significance for condition ($F_{1,82} = 2.093$, $p = .15$), group, ($F_{1,82} = .48$, $p = .48$), or any interaction of condition or group ($F_{1,82} = .34$, $p = .6$).

Exploratory analyses: analysis of other substance exposure

As many of our participants' mothers used substances other than cocaine, repeated measure ANCOVAs were carried out examining amplitude and latency of the FRN and P300 between those whose mothers reported use of THC, alcohol, or nicotine during pregnancy and those who did not. However, no analyses revealed significance for any of the reported substances ($p > .5$).

Table 2. Mean amplitude (uV) and latency (msec) for PCE and NCE adolescents.

	PCE		NCE	
	Amplitude (SD)	Latency(SD)	Amplitude(SD)	Latency(SD)
FRN win	-1.52(2.6)	51.1(3.3)	-1.3(2.3)	51.9(4.4)
FRN draw	-3.1(2.0)	51.67(3.8)	-2.9(2.4)	51.2(3.5)
P300 win	3.6(2.0)	83.04(7.4)	4.0(2.2)	84.3(8.2)
P300 draw	2.7(1.6)	84.5(8.0)	3.6(1.8)	85.7(9.2)

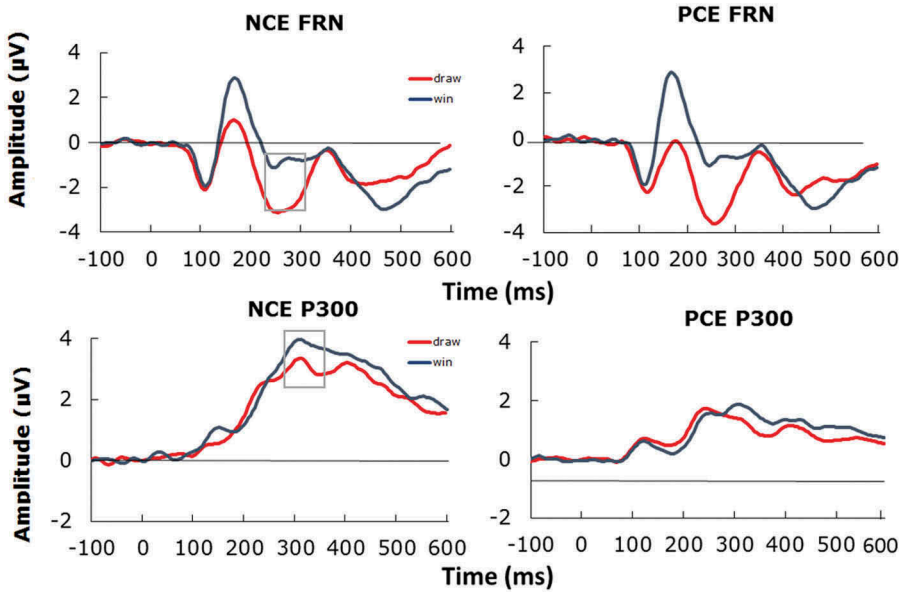


Figure 3. PCE and NCE amplitudes of the FRN (fronto-central) and P300 (central-parietal). The small gray boxes indicate the time windows for analysis for the FRN and P300.

Source analysis

FRN window

A 2-(Condition)-by-5-(region)-by-2-(group) repeated measures ANCOVA was run for source waveforms corresponding to the time window for the FRN. We found a main effect of region ($F_{1,4,82} = 36.20$, $p < .001$, $\eta^2 = .37$), a main effect of condition ($F_{1,4,82} = 7.51$, $p < .01$, $\eta^2 = .55$), and an interaction of condition and region ($F_{1,4,82} = 6.82$, $p < .01$, $\eta^2 = .54$). There was no main effect of group ($F_{1,4,82} = .12$, $p = .71$), and there were no interactions with group ($p > .8$). We examined the condition $\times$ region interaction with post hoc tests that consisted of paired samples t -test of the condition difference effect between regions. A Bonferroni correction was also applied ($p = .01$). Only BA 24, ventral posterior cingulate cortex, did not reach significance between conditions with this correction in place ($p = .02$). The largest difference was present in BA 10, anterior prefrontal cortex.

P300 window. A 2-(Condition)-by-5-(region)-by-2-(group) repeated measures ANCOVA was run for source waveforms corresponding to two time windows for the P300. The first time course was between 300–400 ms, and the ANCOVA revealed a main effect of condition ($F_{1,4,82} = 14.79$, $p < .001$, $\eta^2 = .55$), a main effect of region condition ($F_{1,4,82} = 78.85$, $p < .001$), and an interaction of region and condition ($F_{1,4,82} = 5.61$, $p < .01$). As with the FRN, we examined the condition $\times$ region interaction with post hoc tests that consisted of paired samples t -test of the condition difference effect between regions. A Bonferroni correction was also applied ($p = .01$). Once again, only BA 24, ventral posterior cingulate cortex, did not reach significance between conditions with this correction in place ($p = .02$), and the largest difference was again present in BA 10, anterior prefrontal cortex.

For the second time-course between 400–600 ms, once again, we found a main effect of region ($F_{1,4,91} = 39.12$, $p < .001$, $\eta^2 = .64$), a main effect of condition ($F_{1,4,82} = 14.74$, $p < .01$, $\eta^2 = .14$), and an interaction of condition and region ($F_{1,4,82} = 2.71$, $p < .04$, $\eta^2 = .12$). There was no main effect of group ($F = .24$, $p = .61$), but there was an interaction of group with region ($F_{1,4,82} = 3.20$, $p < .02$, $\eta^2 = .13$), though there was no three-way interaction ($F_{1,4,82} = .95$, $p = .4$). Follow-up

analyses on the group and region interaction revealed that BA 32 (corresponding to dorsal ACC) in the win condition showed greater activity in the NCE group ($M = .047$, $SD = .021$) than the PCE group ($M = .039$, $SD = .020$) ($t = 4.731$, $p < .04$). There were no group differences for the other BA regions for either win or draw conditions ($p > .1$). Figure 4 illustrates the source model centered on BA 32 at 490 ms, showing activity for each group and each condition.

Exploratory analyses: gender. Per a suggestion by a reviewer, we investigated gender as a variable of interest rather than a covariate. A 2-(Condition)-by-2-(gender)-by-2-(group) ANCOVA on the P300 was carried out. For the P300, there was a main effect of gender ($F_{2,4,82} = .457$, $p < .04$) and an interaction of condition and gender ($F_{2,1,82} = 6.22$, $p < .02$). There was no three-way interaction ($p > .3$). Investigation of the interaction revealed that males has significantly larger P300 responses during a win (3.7, $SD = 1.8$) than during a draw (2.8, $SD = 1.7$). Females showed more variability and had more similar amplitudes between win conditions (2.56, $SD = 2.8$) and draw conditions (2.44, $SD = 2.7$).

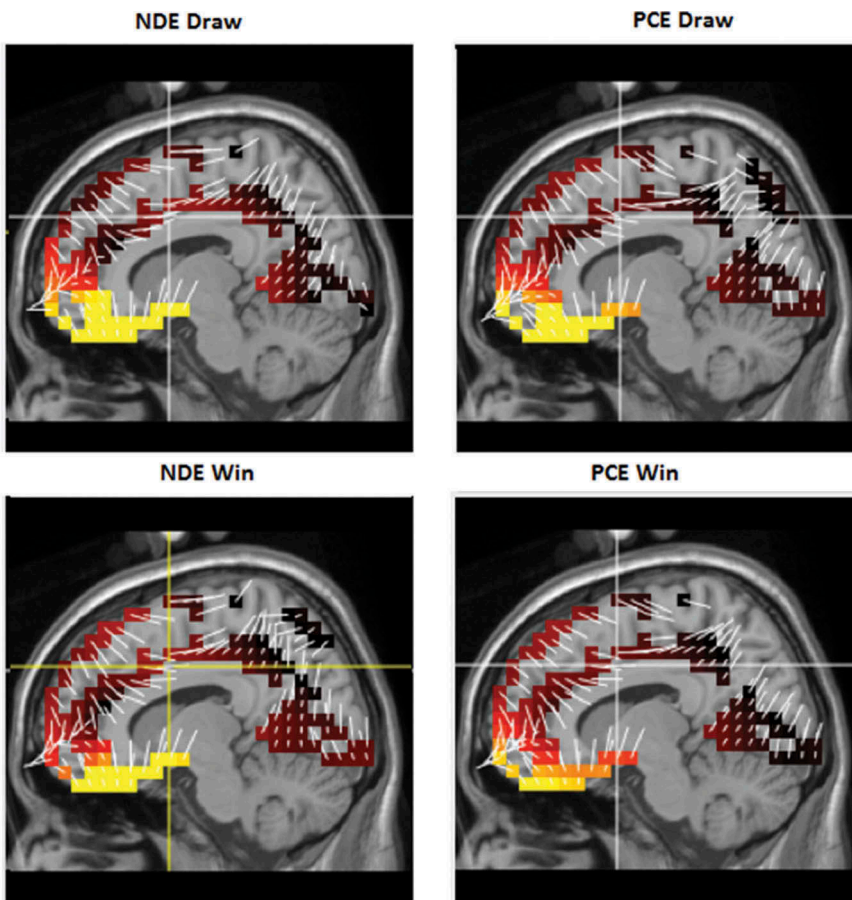


Figure 4. S-low-resolution electromagnetic tomography source models, centered on BA 32 and illustrating each condition for each group at 490 ms in the P300 window.

Discussion

The goal of this study was to investigate how PCE relates to feedback processing in the context of a reward-feedback processing task in an adolescent sample. We recorded ERPs while PCE and NCE adolescents performed a win/draw reward-feedback task. Contrary to our hypothesis, no differences were found for the FRN between the groups, and there were no latency differences found for either the FRN or P300. However, when examining amplitude during the P300 window, we found an interaction of condition and group, suggesting that the P300 amplitude varied by prenatal exposure status and win or draw condition. Specifically, PCE individuals showed smaller p300 amplitudes during a draw condition than did NCE individuals. In addition, source analysis revealed a group-by-region difference in the P300 window, specifically in a region corresponding to the dorsal ACC.

The lack of differences for the FRN is surprising considering the well-established literature on cognitive control in adult cocaine users (Luijten et al., 2014). In addition, younger children with tobacco exposure have been shown to have reduced N2 amplitudes associated with inhibitory control (Boucher et al., 2014). Of course, the major difference here is that our sample was older adolescents exposed to cocaine-prenatally, who, while reporting some initiation of alcohol, tobacco and marijuana, did not report chronic use of cocaine. It is possible that FRN amplitude in this age range is normalized in PCE individuals. This also may be the case for the lack of latency differences. A different sub-sample of the larger PCE cohort ($N = 29$) between the ages of 7 and 9 were reported to have different latencies of the P1, N2, and P3 during a Stroop task when compared to NCE individuals (Mayes et al., 2005). But there were no latency differences noted in our sample at the age of 15–19, potentially implying normalization.

Previous examinations of PCE individuals have established that PCE adolescents engage in more impulsive behaviors (Bridgett & Mayes, 2011), and that these behaviors are associated with poorer executive function (Fisher et al., 2011). PCE individuals also show altered neurodevelopment, including differences in cortical thickness (Gautam, Warner, Kan, & Sowell, 2015) that relates to executive functioning capabilities, including inhibition and cognitive control. Our work suggests that while more automatic feedback error detection may be intact, as evidenced by comparable FRN amplitudes across the groups, differences in neural responses emerged later in processing. However, “mistaken” choices that resulted in no gains differed across PCE and NCE adolescents. During the “draw” condition, our PCE cohort showed smaller P300 amplitudes, which in the context of the game presented can be seen as a failure to win money one could have won. The P300 during decision-making and outcome feedback may be associated with evaluation of probability and estimation of future chances based upon working memory and past experiences (Padron, Fernandez-Rey, Acuna, & Pardo-Vazquez, 2016; Wang et al., 2015). Indeed, smaller P300 amplitudes have been associated with increased cognitive rigidity and poorer performance in tasks of executive function (Dong, Du, & Qi, 2016). As the P300 may represent further processing of the ramifications of choices, a smaller P300 suggests less efficient processing in this domain. Less efficient feedback processing may relate to the impulsive choices and aggression commonly seen in PCE children and adolescents in previous work (Ackerman, Riggins, & Black, 2010), although this possibility warrants direct examination. We did not directly measure cognitive control or impulsivity behaviorally, and future work that examines feedback processing and ERP components associated with it should also measure indices of cognitive control to see if this hypothesized relationship is present.

As the P300 is also sensitive to reward magnitude (Bellebaum et al., 2010; Sato et al., 2005), the lack of further processing of a failure to win money observed in our PCE population may also relate to the relative resistance to negative consequences reported previously in adolescents (Reyna & Farley, 2006). It is possible that PCE individuals perceive negative outcomes as less salient. Another interpretation of the data may be that PCE individuals were simply not as motivated by the reward, and paid little effort in the task. Reduced reward response and a general anhedonia is common in cocaine users (Morie et al., 2014b; Parvaz et al., 2015), and is prevalent enough in stimulant-using populations that it lends evidence to being a vulnerability factor (Leventhal et al., 2010). If PCE

adolescents are not as motivated by the reward, they may not attribute as much effort to the task. This interpretation is strengthened by our identifying the dorsal ACC as the source of the P300 and previous findings indicating this region as being responsible for allocating the correct amount of effort toward control by estimating the value to be gained from the task (Shenhav, Cohen, & Botvinick, 2016).

This group difference in later processing of choice outcomes was also borne out by our investigation into the neural architecture supporting the P300. Source analysis in the time window of the P300 suggested a group difference localized to the dorsal ACC, a region which is commonly associated with monitoring and decision-making over time (Wittmann et al., 2016). This difference was specific to the win condition, suggesting that processing by the dorsal ACC of reward outcomes may be altered in PCE individuals. Future investigations using more spatially sensitive fMRI may shed more light on the neural correlates of the altered feedback processing seen here. In addition, future experiments should examine the specific home lives of PCE children in more detail and assess stressful life events to determine if differences seen in this population are a result of exposure or of environmental factors that accompany such exposure. There were no differences in SES between the NCE and PCE samples in this cohort, but environmental differences may nonetheless exist, and effects of low SES and high stress environments play prominent roles in reward processing (Romens et al., 2015).

Our exploratory gender-based examinations revealed differences between males and females, with males showing stronger P300 differentiation between conditions. This is somewhat consistent with previous work examining this task in a wider range of ages, which found gender differences for the FRN (Crowley et al., 2013) and for the FRN and P300 in a risk-taking task (Crowley et al., 2009). ERP work examining gender differences in feedback processing is scarce, and future studies should examine this issue.

Strengths of this study include the large sample size of PCE adolescents and the use of high-density electrophysiological measures which allow for source analysis. There were several weaknesses, however. One weakness of the study is the fact that some mothers of the PCE individuals used substances other than cocaine. Considering that substance users commonly abuse multiple substances, future work in similar populations should consider other types of substance exposure, including tobacco and cannabis. Another limitation is the prevalence of substance initiation by the PCE individuals, although we did use this data as a covariate in our analyses. In addition, we designed the task to attempt to isolate a negative feedback response that was more independent of the novelty response that may contribute to FRN amplitude when the negative feedback is more unusual or novel. We hoped to get a relatively “clean” investigation of processes related to feedback valence and not to the surprise of a less-common outcome (Hauser et al., 2014). However, the lack of this novelty response may have contributed to our lack of findings between groups for the FRN.

In summary, PCE adolescents demonstrated evidence for altered neural correlates related to feedback processing when compared to NCE adolescents. While the FRN for the PCE group was comparable to that of NCE adolescents, the P300 during the draw condition was smaller in PCE adolescents compared to the NCE group. This finding suggests that later stages of feedback processing, when information about outcomes and decision-making context are used, is impaired in this PCE youth. The dorsal ACC was also implicated as source of altered feedback processing during a win condition. Our results suggest that prenatal substance exposure has effects in adolescence that are specific to the outcome processing stage of decision-making capabilities.

Conflicts of Interest and Disclosures

The authors report no conflict of interest with respect to the content of this manuscript.

Dr. Potenza has consulted for and advised Lundbeck, Ironwood, Shire, INSYS Rivermend Health, Opiant/Lakelight Therapeutics, and Jazz Pharmaceuticals; received research support from the National Institutes of Health, Veteran's Administration, Mohegan Sun Casino, the National Center for Responsible Gaming and its affiliated Institute for

Research on Gambling Disorders, and Pfizer; participated in surveys, mailings, or telephone consultations related to drug addiction, impulse control disorders or other health topics; consulted for law offices and the federal public defender's office in issues related to impulse control disorders; provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; performed grant reviews for the National Institutes of Health and other agencies; has guest-edited journal sections; given academic lectures in grand rounds, CME events and other clinical/scientific venues; and generated books or chapters for publishers of mental health texts. The other authors report no financial relationships with commercial interests.

Funding

Funding for this work included National Institute of Health grants, K01 DA034125 (MJC), T32 MH018268 (MJC), P50 DA09241, UL1-DE19586, RL1 AA017539, R01 DA006025, R01 DA017863, K05 DA020091, T32 DA007238, and R21 DA030665. KPM receives support from MH018268-31 and from K01DA042937, and MNP receives support from the National Center on Addictions and Substance Abuse. Beyond funding, the funding agencies had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

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