Published in final edited form as:

J Psychopharmacol. 2016 April ; 30(4): 370–377. doi:10.1177/0269881115626308.

Effects of Levodopa-Carbidopa-Entacapone and Smoked Cocaine on Facial Affect Recognition in Cocaine Smokers

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Abstract

In addition to difficulties in daily social functioning, regular cocaine users have decrements in social processing (the cognitive and affective processes underlying social behavior) relative to non-users. Little is known, however, about the effects of clinically-relevant pharmacological agents, such as cocaine and potential treatment medications, on social processing in cocaine users. Such drug effects could potentially alleviate or compound baseline social processing decrements in cocaine abusers. Here, we assessed the individual and combined effects of smoked cocaine and a potential treatment medication, Levodopa-Carbidopa-Entacapone (LCE), on Facial Emotion Recognition (FER) in cocaine smokers. Healthy non-treatment-seeking cocaine smokers (N = 14; 2 female) completed this 11-day inpatient within-subjects study. Participants received LCE (titrated to 400mg/100mg/200mg BID) for 5 days with the remaining time on placebo. The order of medication administration was counterbalanced. FER was measured twice during target LCE dosing and twice on placebo: once without cocaine and once after repeated cocaine doses. LCE increased the response threshold for identification of facial fear, biasing responses away from fear identification. Cocaine had no effect on FER. Results highlight the possibility for candidate pharmacotherapies to have unintended impacts on social processing in cocaine users, potentially exacerbating already existing difficulties in this population.

Keywords

facial emotion recognition; cocaine; levodopa; dopamine; social processing

INTRODUCTION

Cocaine use disorders are frequently associated with pronounced difficulties in social and interpersonal functioning (Cunha et al., 2011, Verdejo-Garcia, 2014). Cocaine users are at increased risk of perpetrating (Walton et al., 2002, Macdonald et al., 2008), and being victims (Murray et al., 2008, Cunningham et al., 2009) of violence, including domestic

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COI: The authors have no other conflicts of interest to declare.

violence (Moore et al., 2008), sexual and physical assault (Afful et al., 2010) and homicide (Kuhns et al., 2009). They have high rates of homelessness (Eyrich-Garg et al., 2008) and unemployment (Gfroerer and Brodsky, 1993). Cocaine users are more likely to be unmarried than non-users (Gfroerer and Brodsky, 1993), cocaine use in mothers is associated with loss of child custody (Eiden et al., 2007), and trading sex for drugs is prevalent among both male and female cocaine smokers (Elwood et al., 1997). Thus, cocaine users show indicators of social marginalization and a range of problems in daily social function. While their specific causes remain unclear, these social and interpersonal issues may have important implications for engagement and success in treatment (Preller et al., 2014a, Verdejo-Garcia, 2014).

Although many of these social and interpersonal problems are likely contributed to by the illegality of cocaine, disruptions to social processing, defined here as the cognitive and affective processes underlying social behavior, may also contribute. A growing body of research suggests that regular cocaine use is associated with disrupted function across a variety of social processing dimensions. Compelling recent evidence suggests that regular cocaine users have blunted emotional, physiological, and neural response to socially rewarding stimuli compared to non-users, an effect that is related to the size of their social networks, suggesting that differences in social reward processing have real life implications (Preller et al., 2014a). Both recreational and dependent cocaine users display more self-serving (i.e. unfair) social decision-making in economic games (Hulka et al., 2014) and show blunted emotional empathy (Preller et al., 2014b) compared to healthy controls. Regular cocaine users are less able to recognize fear from pictures of facial affect relative to both non- and occasional cocaine users (Kemmis et al., 2007, Morgan and Marshall, 2013), with no differences observed in identification of other basic facial expressions, or in recognition of complex emotions such as playfulness and jealousy from pictures of the eye region (Kemmis et al., 2007). This preferential difference in fear recognition does not appear to be secondary to clinical confounds such as conduct disorder symptoms or impulsivity (Morgan and Marshall, 2013).

Although these studies have demonstrated social processing difficulties in cocaine users who are not acutely intoxicated, to our knowledge no research has examined the acute effects of cocaine on social cognition or other dimensions of social processing. Given that regular cocaine users are frequently intoxicated with cocaine, acute effects of the drug likely also have a substantial impact on the day-to-day social functioning of cocaine users. Previous reports of transient suspiciousness (Sherer et al., 1988) and paranoia (Kalayasiri et al., 2006, Mooney et al., 2006) after administration of cocaine to cocaine users suggest that, in addition to baseline differences between cocaine users and non-users, cocaine may also acutely alters aspects of social processing, as do some other abused drugs (Bedi et al., 2010, Wardle et al., 2012, Attwood et al., 2012).

In addition to acute effects of cocaine on social processing, little is known about the effects of potential treatment medications on this functional dimension. While there are currently no efficacious FDA-approved medications for cocaine use disorders, a range of potential pharmacotherapies have been assessed in human laboratory (Hart et al., 2008, Hart et al., 2007, e.g. Haney et al., 2010) and clinical studies (Bisaga et al., 2010, Mariani et al., 2012,

Schmitz et al., 2008) for use in cocaine treatment. Although many of these studies assessed non-social cognitive effects of the potential treatment medication, none have examined effects of the medications on social cognition or on other dimensions of social processing. This question is of clinical relevance because effects of treatment medications on social processing could either compound or potentially alleviate the decrements that appear to exist in cocaine users at baseline (see McGregor and Bowen, 2012).

The present study assessed the individual and combined effects of smoked cocaine and Levodopa-Carbidopa-Entacapone (LCE; Stalevo®), a potential medication for cocaine use disorders, on recognition of emotions from others' facial expressions (facial emotion recognition; FER) in regular cocaine users under controlled laboratory conditions. We elected to study FER because it is a social cognitive capacity that is critical to daily function (e.g. see Ekman, 1993). Moreover, FER has previously been shown to be affected by a variety of pharmacological manipulations, with blunted identification of negative facial emotions after administration of drugs such as Δ^9 -tetrahydrocannabinol (THC; Ballard et al., 2012) and 3,4-methylenedioxymethamphetamine (MDMA; Bedi et al., 2010) and enhanced facial fear recognition after acute doses of SSRIs (Harmer et al., 2003, Browning et al., 2007). Data were collected as part of a broader research program investigating the safety and therapeutic potential of dopamine (DA) enhancement for cocaine abuse. Levodopa (l-dopa), which is the immediate precursor of DA, increases synthesis of DA and is used as a treatment for Parkinson's Disease. In LCE, l-dopa is combined with carbidopa and entacapone, both of which inhibit peripheral metabolism of l-dopa, increasing and prolonging the availability of l-dopa centrally (Solla et al., 2010).

Although FER can be assessed with simple accuracy measures (i.e. proportion correct), more insight can be gained by the application of Signal Detection Theory (SDT) to FER data (Stanislaw and Todorov, 1999). The main advantage of using SDT to investigate FER involves the extraction of two independent variables that can contribute to successful FER rates: sensitivity and response bias. Sensitivity is the capacity to detect differences between the 'signal' (trials that contain a particular emotion) and 'noise' (i.e. trials that do not contain that emotion). Response bias is the general tendency to respond 'yes' or 'no' to a particular emotion, where an increased positive response threshold indicates more stringent criteria and more 'no' responses and a decreased positive response threshold indicates more lenient criteria with more 'yes' responses. Changes in accuracy could thus be due to alterations in sensitivity, response bias, or both. Here, we applied SDT to analyses of FER in cocaine users after LCE and cocaine administration. Given evidence of decreased fear recognition in non-intoxicated cocaine users (Morgan and Marshall, 2013, Kemmis et al., 2007) and some findings indicating that recent cocaine use may normalize non-social neuropsychological function in cocaine users (Spronk et al., 2013, Woicik et al., 2009), we hypothesized that cocaine would increase accuracy of fear recognition. An increase in recognition of threat-related emotions such as fear would also be consistent with reports of transient suspiciousness after cocaine (Sherer et al., 1988, Kalayasiri et al., 2006, Mooney et al., 2006). We did not have specific hypotheses about which aspect of fear recognition (sensitivity or response bias) would be altered, or about the effects of LCE on FER.

MATERIALS AND METHODS

Participants

Healthy male and female non-treatment-seeking regular cocaine smokers (reporting cocaine use once weekly and \$30 cocaine/week) between 21 and 50 years old were recruited using newspaper advertisements. During screening, candidates' urine samples were required to test positive for cocaine metabolites to verify cocaine use. We excluded participants who had: 1) current substance dependence other than cocaine or nicotine (DSM-IV criteria; APA, 1994); 2) current major Axis I psychiatric disorders and past psychotic or bipolar disorders (APA, 1994); 3) unstable medical disorders; 4) current pregnancy, lactation, or failure to use effective birth control (females); and 5) concurrent use of medication likely to alter the risk-benefit ratio or affect results (e.g. psychotropic medication). Candidates completed comprehensive medical and psychiatric screening before enrolment and provided written informed consent. After study completion, participants were debriefed and compensated for participation. All procedures were consistent with the 1964 Declaration of Helsinki and approved by the New York State Psychiatric Institute's (NYSPI) Institutional Review Board.

Experimental Protocol

These data were collected as part of a larger, within-subjects, single-blind study investigating the safety of Levodopa-Carbidopa-Entacapone (LCE) (400 mg/100 mg/200 mg), alone and in combination with smoked cocaine, in regular cocaine users.

For 11 days, participants lived on a clinical research unit where illicit drugs were not accessible and medical status could be monitored (see Table 1 for a representative schedule of study events). There were two LCE dosing orders, counterbalanced across participants. Eight participants received four days of placebo (BID) followed by 5 days of active LCE (BID), with two days before discharge to allow for drug clearance. Six participants received 5 days of active LCE (BID) followed by 6 days of placebo (BID). Active LCE treatment was rapidly titrated to a target dose of 400 mg/100 mg/200 mg BID. Baseline FER testing and FER testing during laboratory cocaine administration sessions took place during target LCE dosing (400 mg/100 mg/200 mg BID). LCE (Novartis, New York, NY) was encapsulated by the NYSPI Pharmacy in size 00 capsules with lactose filler. The LCE dose was selected based on previous evidence that the same dose of l-dopa/carbidopa (i.e. 400 mg/100 mg BID) was well tolerated and increased cocaine abstinence in cocaine users (Schmitz et al., 2008).

Participants completed a Facial Emotion Recognition (FER) task 4 times, with 2 measurements occurring during the placebo phase, and 2 during the active LCE phase (see Table 1). Within each medication phase, one FER measurement occurred on a day before the cocaine administration session, with the second FER measurement occurring during a 2.5-hour cocaine administration session. Cocaine sessions involved 6 doses of smoked cocaine (0, 6, 12, 25, 50, 50 mg) administered in ascending order for safety reasons, with administrations spaced at 14-minute intervals to model naturalistic cocaine smoking (Foltin et al., 2003). The NYSPI Pharmacy manufactured smokeable cocaine pellets from cocaine

hydrochloride (Mallinckrodt, St. Louis, Missouri). The cocaine doses selected reliably produce dose-dependent increases in positive affect (Foltin et al., 2003, Reed et al., 2011). Cocaine was smoked in a single inhalation using a glass stem (Foltin et al., 1990). At session initiation and four minutes following each cocaine dose, subjective mood state was recorded and blood was drawn. Research nurses behind a one-way mirror monitored participants constantly during cocaine sessions, continuously monitoring their electrocardiogram (ECG; MAC PC®, Marquette Electronics, Milwaukee, WI, USA). Heart rate (HR) and blood pressure (BP) were recorded every 2 minutes (Sentry II-Model 6100 automated vital signs monitor, NBS Medical, Costa Mesa, CA, USA). Cocaine doses were not administered if cardiovascular signs exceeded safety guidelines (6 minutes of: systolic BP >160 mmHg, diastolic BP >100 mmHg, or HR > [220-participant's age]*.85) or if ECG indicated clinical risk. The FER task was administered immediately following the final (50 mg) smoked cocaine dose, to coincide with expected peak subjective effects.

Outcome Measure

Facial Emotion Recognition task—Facial emotion recognition was measured with a FER task previously shown to be sensitive to other pharmacological manipulations (Bedi et al., 2010). This task measures accuracy identifying fearful, angry, sad, and happy faces (Ekman and Friesen, 1976), morphed from a neutral expression to the prototype emotion (100%) in 10% increments. Faces (N = 170) were presented in randomized order for 500ms, each followed by a prompt for the participant to choose the emotion on the previously displayed face. Our main outcomes were sensitivity to detect each emotion and response bias (an indication of the identification threshold) for each emotion (see Statistical Analyses below). Reaction time (RT) for correct emotion identifications was also measured. In addition, participants rated a subset of stimuli (N = 26) for how threatening they perceived the face to be, on a Likert-type scale from 1 (not at all threatening) to 9 (extremely threatening). Threat ratings were included because acute cocaine administration can produce feelings of paranoia (Mooney et al., 2006), potentially leading to increased threat ratings of facial expressions. Stimuli for threat ratings were the prototype emotion (100%) pictures for each of the four emotions, plus neutral face stimuli. The outcome measure was the mean threat rating; we also assessed RT for threat ratings.

Subjective Effects of Cocaine—Subjective mood during cocaine sessions was assessed at baseline (0 minutes), four minutes after each cocaine dose (+ 4 mins; + 18 mins; + 32 mins; + 46 mins; + 60 mins; +74 mins), and 34 and 64 minutes after the last dose (+ 104 mins; +134 mins). Mood was measured using Visual Analogue Scales (VAS) in which participants were asked to rate the extent to which a series of mood adjectives (e.g. 'confused', 'social', 'alert') or drug effects (e.g. 'high', 'sedated') described how they felt at that moment. VAS were 100mm long and anchored with 'Not at all' and 'Extremely'. There were 26 items. Previous cluster analyses of these items to assess subjective cocaine effects yielded five clusters (Evans et al., 2002). For the present analyses, subjective effects were only used to confirm that LCE administration did not alter baseline mood state and that cocaine administration produced expected dose-related subjective effects. To confirm that LCE did not alter baseline mood state, we used two of the VAS cluster scales: the first corresponding broadly to Negative Affect and comprising: 'Anxious', 'Bad Drug Effect',

‘Confused’, ‘Depressed’, ‘Irritable’, ‘Sedated’, and ‘Tired’, and the second corresponding to Positive Affect/Sociability and including ‘Alert’, ‘Focused’, ‘Self-confident’, ‘Social’, and ‘Talkative’. Cluster scores were calculated as the mean of these items. We also assessed for any effects of LCE on baseline cocaine craving using a single VAS item: ‘I want cocaine’. To ensure that cocaine had expected positive mood effects, we used a single VAS item: ‘Good Drug Effect.’

Statistical Analyses

Accuracy of emotion identification was assessed using Signal Detection Theory (SDT) based analyses, with two outcome measures employed: d' , a measure of participants' sensitivity to detect differences between trials for each emotion (signal trials) and trials that do not contain that emotion (noise trials), and β , a measure of response bias or the tendency to respond yes or no to any given emotion (Stanislaw and Todorov, 1999). d' was calculated as $d' = \phi^{-1}(H) - \phi^{-1}(F)$ where H is the hit rate (number of correct classifications divided by total trial number for each emotion category) and F is the false alarm rate (Stanislaw and Todorov, 1999, number of false alarms divided by the total number of possible false alarms; MacMillan, 1993). β was calculated as $\beta = e^{[(\phi^{-1}(F))^2 - (\phi^{-1}(H))^2]/2}$ (Stanislaw and Todorov, 1999). Extreme values for H and F were replaced with $0.5/n$ for 0 and $(n-0.5)/n$ for 1, where n is the number of signal or noise trials (Stanislaw and Todorov, 1999). d' and β were entered into 3-way repeated measures ANOVAs, with LCE (LCE/placebo) as one factor, cocaine (cocaine/placebo) as the second, and emotion (fear, anger, sadness, happiness, and neutral) as the third. Significant interactions were followed up with simple main effects analyses and posthoc pairwise comparisons. The significance threshold was set at 0.05. We also conducted 3-way repeated measures ANOVAs on RT for FER responses, mean threat ratings, and RT for threat ratings, with LCE (LCE/placebo), cocaine (cocaine/placebo), and emotion (fear, anger, sadness, happiness, and neutral) as the factors. We planned to follow significant interactions with simple main effect analyses. Where Mauchly's test of sphericity indicated violation of the assumption of sphericity ($p < .05$), we interpreted Greenhouse-Geisser corrected degrees of freedom and significance levels. For accuracy measures and threat ratings, only responses with RTs greater than 200ms were included to exclude anticipatory errors (e.g. see Ratcliff, 1993); this led to removal of less than 2% of total data points. For RT analyses, we included only correct items (for facial emotion recognition); we also excluded items with RTs less than 200 ms or greater than 3.29 standard deviations (SD) from drug condition means (see Ratcliff, 1993); this resulted in removal of less than 3% of data points. Three participants had variations from protocol regarding FER testing (two completed FER testing on cocaine after the first rather than the second 50 mg dose of cocaine and one completed a second cocaine session during the placebo LCE phase because she failed to inhale the smoked cocaine during the first session). Removal of these participants' data did not alter the FER results; these data were therefore retained. Cocaine subjective effects were analyzed using repeated measures ANOVA with LCE as one factor and time as the second. Significant main effects of time were probed using pairwise comparisons between each time-point and baseline measures. Effects of LCE dose on baseline mood state and cocaine craving were assessed using paired t -tests. Prior to analyses, data were examined for univariate outliers. Isolated outlying data points were observed; these points were truncated to $z = 3.29$ (see Tabachnick and Fidell, 2013). Effect

sizes are presented as partial η^2 . Although it is difficult to estimate power when using more complex statistics such as the 3-way repeated measures ANOVA employed herein, post-hoc analyses using G*Power (Faul et al., 2007) estimated that with a sample size of 14, an alpha-level of 0.05, and power of 0.8 in a repeated-measures design, this study was adequately powered to detect medium to large effect sizes, i.e. partial η^2 values of approximately 0.1 and above. Analyses were conducted with SPSS Statistics 20 (IBM, Armonk, NY).

RESULTS

Participants

Fourteen participants (12 male; 2 female) who were on average 45.4 (SD = 2.9) years of age completed the study. At intake, all participants reported smoking cocaine; six also reportedly used cocaine via the intranasal route. Volunteers reported using cocaine 3.7 (SD = 2.5) days per week and spending \$177.86 (SD = 145.27) per week on average. Twelve were current tobacco cigarette smokers, smoking an average of 7.4 (SD = 5.7) cigarettes per day. Nine reported past month alcohol consumption, drinking on 2.2 (SD = 2.2) days per week. Two reported smoking marijuana 1.5 (SD = 0.0) days weekly in the past month. One participant reported current heroin use once per week. Ten participants met DSM-IV criteria for current Cocaine Dependence at study entrance. Nine participants identified as Black, 4 as White (two of these were Hispanic) and 1 as mixed race (White, Black, and Native American).

Effects of LCE and Cocaine on Emotion Recognition: Response Bias and Sensitivity

There was an interaction effect between LCE condition and emotion type on response bias measured with β ($F(2.1,26.9) = 4.2, p = 0.025$, partial $\eta^2 = 0.24$). Follow-up analysis by emotion category revealed that LCE significantly increased β values for fear identification ($F(1,13) = 7.2, p = 0.02$; partial $\eta^2 = 0.36$; see Figure 1 top panel). Larger β values indicate a higher threshold for identifying a face as fearful. There was no effect of cocaine or interaction between LCE and cocaine on β values for fear (p values > 0.45). There were no other effects of LCE, cocaine, or interactions between them on β values for anger, sadness, happiness, or neutral facial expressions (all p values > 0.19).

In addition to the interaction of LCE and emotion type, there was a trend towards a main effect of LCE ($F(1,13) = 4.3, p = 0.06$, partial $\eta^2 = 0.25$) such that β values overall tended to be higher on LCE than placebo. Given the interaction between emotion type and LCE condition, however, this seems likely to be due to the effect of LCE on response bias for fear identification (see Figure 1, top panel). There was a main effect of emotion ($F(1.9,24.9) = 8.7, p = 0.002$, partial $\eta^2 = 0.40$) on β values, with values lower for neutral faces than for angry, fearful, happy, and sad faces and lower for angry than for happy, fearful, and sad faces. There were no other main or interactive effects on response bias (all p values > 0.59).

There was a main effect of emotion type on sensitivity of emotion recognition (d' : $F(2.5,33.0) = 44.0, p < 0.001$, partial $\eta^2 = 0.77$), with participants showing more sensitivity to happy faces than all other emotions, more sensitivity to fear and anger than neutral or sad faces, and more sensitivity to sad than neutral facial emotions (see Figure 1, bottom panel).

There were no main or interaction effects of LCE or cocaine on d' values (all p values 0.15).

Effects of LCE and Cocaine on Threat Ratings and Reaction Times

There was a main effect of Emotion type on threat ratings ($F(1.6,21.0) = 23.4, p < 0.001$, partial $\eta^2 = 0.64$) such that angry faces were rated as more threatening than all other emotions, fearful faces were rated more threatening than happy, neutral or sad faces, sad faces were more threatening than happy faces, and neutral were more threatening than happy expressions. There were no significant main or interaction effects of LCE or cocaine on threat ratings for facial stimuli (all p values 0.30).

There was a main effect of Emotion type on RT for FER ($F(4,44) = 19.2, p < 0.001$, partial $\eta^2 = 0.64$), with correct fear identification taking longer than identification of anger, happy, and neutral faces, sadness taking longer than identification of neutral and happy faces, and anger taking longer than neutral and happy face identification. There were no other significant main or interaction effects on RT for accurate FER responses (all p values 0.08).

There was a main effect of Emotion type on RT for threat ratings ($F(2.1,27.7) = 4.4, p = 0.021$, partial $\eta^2 = 0.25$), with threat ratings for fearful, angry, sad, and happy faces taking longer than those for neutral faces. There were no other significant main or interaction effects of LCE or cocaine on RT for threat ratings (all p values 0.19).

Subjective Mood State

As expected, cocaine significantly increased ratings of Good Drug Effect in a dose-dependent fashion ($F(1.9,24.2) = 18.6, p < 0.001$, partial $\eta^2 = 0.25$; see Figure 2). There was no main effect of LCE or interaction between LCE and cocaine on ratings of Good Drug Effect (p 's 0.78). There was no difference in baseline mood state (Negative Affect or Positive Affect/Sociability) or cocaine craving at the beginning of cocaine sessions in active versus placebo LCE dosing, indicating that LCE alone did not alter mood or cocaine craving (all p values 0.15).

DISCUSSION

Contrary to our hypothesis, there was no acute effect of cocaine administration on facial affect recognition in these regular cocaine smokers. Conversely, the candidate treatment medication LCE preferentially reduced identification of fearful facial expressions without altering recognition of other emotions in regular non-treatment-seeking cocaine users. This effect was observed as a response bias away from identifying faces as fearful, with no effect on sensitivity to detect fear (i.e. signal) among other facial expressions (i.e. noise). Of note, this effect occurred without any changes in subjective mood state after LCE, suggesting that it was not due to mood alterations such as reduced anxiety (which could be associated with decreased recognition of threat-related emotions in others). There were no interactive effects of cocaine and LCE on FER in this population.

The observed effect of LCE on facial fear recognition should be interpreted cautiously, given the small sample size and the fact that this effect was not hypothesized *a priori*. However, the current findings suggest that further investigation of the effects of LCE on FER in cocaine users is warranted. Should these effects be replicated in further research, they may have clinical implications if this medication is demonstrated to be clinically efficacious for cocaine use disorder. Regular cocaine users in the non-intoxicated state have a variety of alterations to social processing, including reduced fear recognition, when compared to non-using controls and occasional users (Kemmis et al., 2007, Morgan and Marshall, 2013). Our findings suggest that, in addition to desired effects of DA medications such as LCE on cocaine use, a possible unintended consequence may be the exacerbation of already existing social processing difficulties. As noted above, cocaine abusers demonstrate functional problems across a range of social and interpersonal domains (e.g. see Cunha et al., 2011, Verdejo-Garcia, 2014, Eiden et al., 2007, Walton et al., 2002, Macdonald et al., 2008), which may be contributed to by disrupted social processing. The extent to which changes such as those produced by LCE would further impair daily social functioning is unclear. However, previous research has shown that performance on laboratory FER measures track with self-reported interpersonal problems in other drug abusing populations (Kornreich *et al.*, 2002), suggesting that these changes could have implications in terms of daily social functioning. Further assessment of the effects of LCE on FER in cocaine abusers could thus also valuably assess impacts on daily social function, with a view to determining whether behavioral remediation of social cognitive decrements may be indicated in cocaine users being treated with LCE.

Despite reports of transient feelings of suspiciousness or paranoia after cocaine (Sherer et al., 1988, Kalayasiri et al., 2006, Mooney et al., 2006), we did not observe changes in FER or facial threat perception consistent with such effects. Indeed, repeated doses of smoked cocaine had no effect on FER or ratings of threat from emotional faces. There are several possible reasons for the absence of changes consistent with suspiciousness. It is possible that these effects only occur in subgroups of cocaine users, who were potentially not represented in this sample. Alternatively, such effects may only become apparent with repeated binge doses of cocaine, a pattern of use commonly observed among regular cocaine smokers (Vosburg et al., 2010). Although our laboratory cocaine administration paradigm is designed to mimic this pattern of repeated dosing, the amount of cocaine administered is limited by safety concerns. Thus, it is unclear if higher or more doses of cocaine might produce FER alterations. The cocaine doses administered were, however, sufficient to result in robust increases in ratings of good drug effect (see Figure 2). Finally, it is possible the measure was not sufficiently sensitive to detect drug-related increases in suspiciousness. We are unaware of any behavioral measures validated for detecting such effects; development and validation of such paradigms could be an important avenue for future research.

As an initial attempt to measure the effects of LCE and cocaine on FER in cocaine users, there were limitations to this study. For instance, the sample size was small. Although this is consistent with other studies of acute effects of cocaine (Vosburg et al., 2010, Reed et al., 2009, Reed et al., 2011), this may have impacted the results by limiting power to detect subtle effects. The sample included only 2 women (and 12 men), precluding examination of

sex differences in the effect of the drug conditions on FER in this population. Given evidence of sex differences in social cognition (Williams et al., 2009), this would be an important future research direction. A third limitation was that cocaine administration was not placebo controlled and the order of non-cocaine and cocaine sessions was not balanced, with non-cocaine FER testing always occurring before FER testing after cocaine. Moreover, we repeated the FER test 4 times within the study, leaving open the possibility of learning effects, or effects on motivation. To assess this possibility, we examined the effects of session order on the outcome measures. Although reaction times became quicker with repeated testing, there was no effect of session order on d' or beta measures, or on threat ratings, suggesting that despite the limitations of repeated testing, this approach did not unduly affect the results. However, given the absence of a placebo cocaine condition, we cannot completely rule out the possibility of cocaine effects on this task. Finally, the study was single blind; research staff was aware of drug conditions. This limitation was to ensure safety, as this was the first study to assess combined administration of LCE and smoked cocaine.

These limitations notwithstanding, the current findings contribute to an emerging body of evidence indicating potentially clinically-relevant alterations to social processing after a range of pharmacological manipulations (Harmer et al., 2009, Harmer, 2008, Norbury et al., 2007, Bedi et al., 2010, Bedi et al., 2009). Maintenance on LCE, the direct precursor of dopamine, decreased facial fear recognition by increasing the response threshold for identifying faces as fearful in regular cocaine smokers. Given the importance of social relationships as alternative reinforcers for individuals with drug use disorders (e.g. see McGregor and Bowen, 2012) and possible negative effects of social difficulties on treatment (Gainey et al., 1993, Lovaglia and Matano, 1994), these findings highlight the importance of assessing for unintended drug effects on social processing when testing candidate treatment medications for cocaine and other drug use disorders.

Acknowledgements

The authors would like to thank the volunteers for participating and Paula Askalsky for assistance in data collection. The research described in this manuscript complies with the laws of the country in which it was performed (USA).

Funding: This work was supported by the National Institute on Drug Abuse (DA09236, DA022412, and DA034877). Dr. Nunes has received: medication for research studies from Alkermes/Cephalon, Inc. and Reckitt-Benckiser; medication for a research study in data analysis from Duramed Pharmaceuticals; a web-based behavioral intervention for a research study in data analysis from HealthSim, LLC; and devices under investigation and reimbursement for travel expenses for investigators' meeting from Brainsway. He was paid an honorarium and received reimbursement for travel expenses for attendance at a Lilly Advisory Board Meeting in January 2012 and received educational materials from Otsuka America Pharmaceutical, Inc. in 2013.

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Figure 1.

Top Panel. Effects of LCE (Levodopa/Carbidopa/Entacapone 400 mg/100 mg/200 mg BID) and cocaine (6, 12, 25, 50, 50 mg before testing) on response bias, assessed with β . Data are means ($\pm$ SEM). There was a main effect of LCE on β values for facial fear recognition, such that values on LCE were higher than those on placebo. Higher β values indicate an increased threshold for identifying faces as fearful (i.e. more 'no' responses). LCE = Levodopa/Carbidopa/Entacapone; PBO = placebo LCE treatment; Baseline = Testing without cocaine administration; Post Cocaine = Testing after acute cocaine administration; asterisk denotes

significant difference from placebo ($p < 0.05$). Bottom Panel. Effects of LCE and cocaine on sensitivity to emotional faces, assessed with d' . Sensitivity varied between emotion types, with d' higher for happy than all other emotional categories, higher for fear and angry than neutral and sad faces, and higher for sad than neutral faces. There were no effects of LCE or cocaine on sensitivity to facial emotions.

Figure 2.

Ratings of “Good Drug Effect” during cocaine administration sessions as a function of time (collapsed across placebo and LCE cocaine administration sessions). Placebo cocaine was administered at 0 minutes. Active cocaine doses (6, 12, 25, 50, 50 mg in ascending order) were administered at 14, 28, 42, 56, and 70 minutes. The facial emotion recognition task was started at 80 minutes. BL = baseline. Data are means ($\pm$ SEM). Asterisks denote significant difference from baseline ($p < 0.05$).

Table 1

Study Design: Representative Schedule for Medication and Facial Emotion Recognition Testing

Day	Drug Condition	Study Procedures	LCE dose	
			AM	PM
1		Hospital admission		0
2			0	0
3			0	0
4	PBO LCE No Cocaine	FER testing – no cocaine	0	0
5	PBO LCE Cocaine	Cocaine session in AM: FER testing	0	100/25/200
6			100/25/200	100/25/200
7			200/50/200	200/50/200
8	Active LCE No Cocaine	FER testing – no cocaine	400/100/200	400/100/200
9	Active LCE Cocaine	Cocaine session in AM: FER testing	400/100/200	100/25/200
10			0	0
11			0	0
12		Final assessment and discharge		

PBO = placebo; LCE = levodopa/carbidopa/entacapone; FER = Facial Emotion Recognition