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Atypical valuation of monetary and cigarette rewards in substance dependent smokers

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HIGHLIGHTS

- Non-drug relative to drug-related rewards were compared using the reward positivity.
- Cigarette relative to monetary rewards elicited a larger reward positivity.
- Obtaining drug-related rewards engages the anterior cingulate cortex (ACC) to exert control over behaviors in substance dependent (SD) individuals.

ABSTRACT

Objective: Substance dependent (SD) relative to non-dependent (ND) individuals exhibit an attenuated reward positivity, an electrophysiological signal believed to index sensitivity of anterior cingulate cortex (ACC) to rewards. Here we asked whether this altered neural response reflects a specific devaluation of monetary rewards relative to drug-related rewards by ACC.
Methods: We recorded the reward positivity from SD and ND individuals who currently smoke, following an overnight period of abstinence, while they engaged in two feedback tasks. In a money condition the feedback indicated either a monetary reward or no reward, and in a cigarette condition the feedback indicated either a drug-related reward or no reward.
Results: Overall, cigarette relative to monetary rewards elicited a larger reward positivity. Further, for the subjects who engaged in the money condition first, the reward positivity was smaller for the SD compared to the ND participants, but for the subjects who engaged in the cigarette condition first, the reward positivity was larger for the SD compared to the ND participants.
Conclusions: Our results suggest that the initial category of feedback "primed" the response of the ACC to the alternative feedback type on subsequent trials, and that SD and ND individuals responded differently to this priming effect.
Significance: We propose that for people who misuse addictive substances, the prospect of obtaining drug-related rewards engages the ACC to exert control over extended behaviors.

1. Introduction

Neurocognitive alterations to mesocorticolimbic reward function by drugs of abuse are thought to facilitate a progression towards excessive drug use (Schultz, 2011; Redish et al., 2008). Much attention in the field has focused on the contributions of subcortical brain regions such as the ventral striatum to drug-induced changes to behavior (Volkow et al., 2007). Although there is compelling evidence that cortical brain regions, including orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex (ACC), and insula, are also heavily involved (Hyman et al., 2006), their contribution to this process is relatively less explored. Here we focus on the role of the ACC in substance dependence. The function of ACC is highly debated, but we have recently proposed that the ACC utilizes dopamine reward signals to learn the value of extended, context-specific sequences of behavior directed toward particular goals (Holroyd and McClure, 2015; Holroyd and Yeung, 2012). This theoretical framework suggests that the

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ACC may be centrally concerned with regulating goal-directed behaviors underling substance use and misuse.

In humans, the reward processing function of ACC can be investigated using a component of the event-related brain potential (ERP) called the reward positivity (also called the feedback-related negativity; for reviews see Walsh and Anderson, 2012; Sambrook and Goslin, 2015). We have previously proposed that the reward positivity is produced by the impact of reward prediction error signals (RPEs) carried by the midbrain dopamine system onto motor areas in ACC, where they are utilized for the adaptive modification of behavior according to principles of reinforcement learning (Holroyd and Coles, 2002). RPEs constitute the learning term in powerful reinforcement learning algorithms that indicate when events are "better" or "worse" than expected (Sutton and Barto, 1998). Over the past two decades substantial evidence has supported the proposition that RPE signals are encoded in the brains of humans and other animals as phasic increases and decreases of midbrain dopamine neuron activity (Schultz, 2010), and numerous reward positivity studies have elucidated how the ACC processes dopamine-like RPE signals in both normal (Walsh and Anderson, 2012; Sambrook and Goslin, 2015) and atypical (Proudfit, 2015) populations.

Notably, we demonstrated across a series of studies that young adults meeting criteria for substance dependence exhibited an attenuated reward positivity to stimuli indicating small monetary gains, suggesting that they value such rewards as if they were non-rewarding (Baker et al., 2011, 2015a). Because the dependency measure was sensitive to polydrug use – such that the affected population tended to misuse a broad range of substances including alcohol, nicotine, and cannabis – the smaller reward positivity appears to reflect a general reward processing impairment that cuts across specific drug types. If the ACC is indeed responsible for the selection and execution of extended, goal-directed behaviors, as proposed (Holroyd and McClure, 2015; Holroyd and Yeung, 2012), then our finding of reduced reward positivity amplitude suggests abnormal goal-directed behavior in this population, whether as a consequence of the drug use itself, a preexisting vulnerability, or both (Baker et al., 2011, 2015a).

An unresolved question concerns whether the reduced reward positivity in substance dependent (SD) individuals reflects a global impairment in reward processing that affects all types of rewards, or a specific devaluation of non-drug-related compared to drug-related rewards (Ahmed, 2004, 2005; Ahmed et al., 2002). In regards to the latter possibility, enhanced valuation of drug-related cues could bias the ACC to select extended behaviors that ultimately converge on drug use in lieu of other behaviors directed toward non-drug related goals. Alternatively, a blunted response by ACC to rewards in general – whether drug-related or not – would suggest decreased effortful pursuit of a wide range of rewarding behaviors. These disparate possibilities would point toward distinct avenues for the study and treatment of substance dependence.

To investigate this issue, we examined whether the abnormal reward positivity observed in SD individuals reflects impaired reward valuation per se or a specific devaluation of small monetary rewards relative to drug-related rewards. To do so, we replicated a previous study that demonstrated that SD individuals, relative to non-dependent (ND) individuals, produce a smaller reward positivity to feedback indicating small monetary rewards (Baker et al., 2011). As before, the level of substance dependence was determined according to participant responses to an inventory that assesses problematic substance use aggregated across a broad range of addictive substances including tobacco, alcohol, cannabis, and other drugs. Crucially, in addition to the standard condition in which the feedback indicated that subjects either would or would not earn 5 cents for that trial, we included a second condition in which the feedback indicated that subjects either would or would not earn a drug-related reward for that trial. But because alcohol and illicit drugs were not advisable for this sample of undergraduate students, we adopted nicotine as a drug reward that would be of interest to polysubstance users. To increase craving for the reward, participants were asked to abstain from smoking for the 24 h preceding the study; compliance was verified by measuring participant carbon monoxide (CO) levels. In short, we screened for SD and ND individuals who currently smoke, and following an overnight period of abstinence, recorded the reward positivity to feedback indicating forthcoming drug-related and non-drug related rewards in the same individuals.

We specifically examined 3 questions. First, because the reward positivity to drug-related feedback stimuli has not yet been investigated, we examined whether or not cigarette-related rewards elicit this ERP component. Second, we tested whether, consistent with our previous findings, feedback stimuli indicating small monetary rewards would elicit an attenuated reward positivity in SD compared to ND individuals. Third, we asked whether drug-related rewards would normalize this impairment in SD individuals. We predicted that if feedback stimuli indicating potential puffs on a cigarette increased reward positivity amplitude for SD individuals, then the ACC would appear to devalue the pursuit of small monetary rewards relative to drug-related rewards in this sample. Alternatively, if the reward positivity to drug-related feedback were also attenuated, then ACC function would appear broadly impaired in this population.

2. Methods

2.1. Participants

Participants were recruited from the University of Victoria Department of Psychology subject pool. Each subject received course credit for their participation in a two-session study spanning a 1–2 week interval. They were required to be current smokers who were not currently trying or planning to quit smoking. All participants had normal or corrected-to-normal vision and all gave informed consent. The study was approved by the local research ethics committee and was conducted in accordance with the ethical standards prescribed in the 1964 Declaration of Helsinki.

For the purpose of replicating our previous study (Baker et al., 2011, 2015a), participants were classified as either SD or ND according to their scores on the Global Continuum of Substance Risk (GCR) scale of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), a validated screening test that uses DSM-specific criteria for identifying the degree of problematic substance use across a range of drugs (i.e., tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants, sedatives, hallucinogens, inhalants, opioids and "other drugs") (Humeniuk et al., 2008). Specifically, participants with GCR scores falling within the bottom (score < 22) and top (score > 39) quartiles of our sample were classified as ND (12 participants) and SD (12 participants), respectively. These scores are comparable with the cut-offs established in previous validation studies of the ASSIST for non-dependence (score < 15) and dependence (score > 39.5) (Newcombe et al., 2005), as well as in our previous studies (ND: score < 16, $n = 18$; and SD: score > 41, $n = 18$, Baker et al., 2011; see also Baker et al., 2013, 2015a).

2.2. Procedures

Informed consent, questionnaire data, and a baseline measure of breath carbon monoxide levels (see below) were obtained from participants during Session 1; the EEG data were collected during

Session 2. During Session 1, current smoking status was confirmed by assessing breath CO levels (Benowitz, 2002) using a piCO+ Smokerlyzer carbon monoxide breathalyzer (Bedfont Scientific Ltd., Harrietsham, Maidstone, Kent, England). Participants were then asked to complete a set of computer-based questionnaires used in our previous studies (Baker et al., 2011, 2015a). The computer-based survey was comprised of several separate inventories, namely, the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (Humeniuk et al., 2008), the Severity of Alcohol Dependence Questionnaire (Stockwell et al., 1993), Winnipeg Health and Drinking Survey – questions pertaining to family history of substance abuse (Barnes and Murray, 1989), the Addiction-Prone Personality (APP) Scale (Anderson et al., 1999), and the Substance Use Risk Profile Scale (SURPS) (Conrod and Woicik, 2002). The degree of nicotine dependence (0–3: low, 4–15: moderate, 16–20: dependence) was assessed using the Specific Substance Involvement Score of the tobacco category of the ASSIST. Finally, subjects completed a paper-and-pen tobacco craving questionnaire (TCQ), a 47-item scale that assesses state levels of craving (Heishman et al., 2003). All inventories were administered and scored according to their guidelines. Upon completing the questionnaires, participants engaged in a decision making task (Frank and Seeberger, 2004), the results of which will be reported elsewhere. Data pertaining to severity of alcohol dependence, personality, and family history were not used in the present analysis. At the end of Session 1, participants were asked to abstain from smoking for 24 h prior to the start of Session 2.

Session 2 commenced within two weeks following Session 1. Subjects were asked again to provide their CO levels (measured in parts per million; ppm) and to complete the TCQ. Because smokers often misclassify their smoking behavior (Noonan and Duffy, 2014), compliance with the 24 h abstinence period was defined as breath CO < 13 ppm, in keeping with prior work (Perkins et al., 1994). The piCO+ Smokerlyzer device is valid and reliable indicator of smoking status used to identify recent (i.e., past-day) smoking behavior (Benowitz, 2002). CO can remain in the bloodstream for up to 24 h, and after 48 h smokers and non-smokers exposed to the same environment exhibit the same CO levels (Deveci et al., 2004). Those failing to meet this criterion were allowed to return later the same week for a second attempt to complete the session ($n = 4$).

Participants engaged in a virtual T-maze guessing task that we used in our previous reward positivity studies of SD (Baker et al., 2011, 2015a). Stimuli were presented and responses recorded using E-Prime (Psychological Software Tools, Pittsburgh, PA). In brief, participants completed both a "money condition" and a "cigarette condition" of the virtual T-Maze task (Fig. 1), the order of which were counterbalanced across subjects. In the money condition, participants were told that presentation of the reward stimulus indicated that the selected alley contained 5 cents (reward feedback), and that the presentation of the No-reward stimulus indicated that the alley they selected was empty (no-reward feedback). In the cigarette condition, participants were told that the reward stimulus indicated an opportunity for 5% of a single, 3 s-long puff on a cigarette (Perkins et al., 1994), whereas each no-reward stimulus indicated that such an opportunity had been missed. Three blocks, consisting of 50 trials per block, composed each condition. To emphasize the size of these rewards, participants were shown cigarettes cut in lengths ranging from a 1 s-long puff to a full cigarette (equivalent to about 7 puffs or 130 wins). As with the previous study, unbeknownst to the subjects the feedback stimuli occurred randomly and with equal probabilities; subjects earned approximately $3.75 in the control condition and four 3 s-long puffs in the cigarette condition (i.e., more than half a cigarette). Each block was separated by a self-paced rest break at which time participants were shown either the percentage of puffs or the money they had earned, depending on the condition. Each condition lasted roughly 15 min.

After the task was completed, participants were again asked to complete the decision making task (Frank and Seeberger, 2004; Baker et al., 2013). The EEG cap was then removed and participants were escorted to a smoking-designated area on campus where they were provided with an opportunity to consume their accumulated puffs (rounded up to one cigarette, selected by the participant from two premiere cigarette brands) under close observation of the investigator. To ensure that the reward feedback stimuli in the cigarette condition were sufficiently motivating, they were required to return to the laboratory and remain there without further smoking for one hour following task completion (Perkins et al., 1994). During this period they were asked to complete the decision making task a third time (Frank and Seeberger, 2004). Finally, subjects again provided CO levels with the Smokerlyzer.

2.3. EEG data acquisition and analysis

2.3.1. Data acquisition

Continuous EEG was recorded from 36 scalp electrodes (Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, FT9, FC5, FC1, FCz, FC2, FC6, FT10, T7, C3, Cz, C4, T8, TP9, CP5, CP1, CPz, CP2, CP6, TP10, P7, P3, Pz, P4, P8, PO7, POz, PO8, Oz) placed according to the 10/20 system (Jasper, 1958). Two electrodes were also placed on the left and right mastoids and the ground electrode was placed on the front-central region of the scalp (corresponding to AFz). For the purpose of artifact correction the horizontal electrooculogram (EOG) was recorded from the external canthi of both eyes, and vertical EOG was recorded from the sub-orbit of the right eye and electrode channel Fp2.Data were recorded with a 64-channel Quick Amp amplifier (Brain Products, Munich, Germany) and referenced online to an average reference including all electrodes, and later re-referenced offline to a combined mastoid reference. Signals were acquired using Ag/AgCl ring electrodes mounted in a nylon electrode cap with a conductive gel (Falk Minow Services, Herrsching). Signals were amplified by low-noise electrode differential amplifiers with a frequency response of DC 0.017–67.5 Hz (90 dB octave roll off) and digitized at a rate of 250 samples per second. Digitized signals were recorded to disk using and Vision Recorder software (version 2.0, Brain Products, Munich, Germany). Inter-electrode impedances were maintained below 10 KΩ.

2.3.2. Data analysis

Post-processing and data visualization were performed using Brain Vision Analyzer software (Brain Products GmbH, Munich). The digitized signals were filtered using a 4-th order digital Butterworth filter with a passband of .10–20 Hz. An 800 ms epoch of data extending from 200 ms prior to 600 ms following the onset of each feedback stimulus was extracted from the continuous data file for analysis. Ocular artifacts were corrected using the eye movement correction algorithm (Gratton et al., 1983). The EEG data were re-referenced to the average voltage recorded at the mastoids electrodes. The data were baseline corrected by subtracting from each sample the mean voltage associated with that electrode during the 200 ms interval preceding stimulus onset. Muscular and other artifacts were removed using a ±150 μV level threshold and a ±35 μV step threshold as rejection criteria. ERPs were then created for each electrode and participant by averaging the single-trial EEG according to feedback type (Reward, No-reward). Reward positivity amplitude was then determined by identifying the maximum absolute amplitude of the difference wave within a 200–400 ms window following feedback onset. For the purpose of statistical analysis, reward positivity was evaluated at channel FCz, where it reaches maximum absolute amplitude (Miltner et al., 1997);

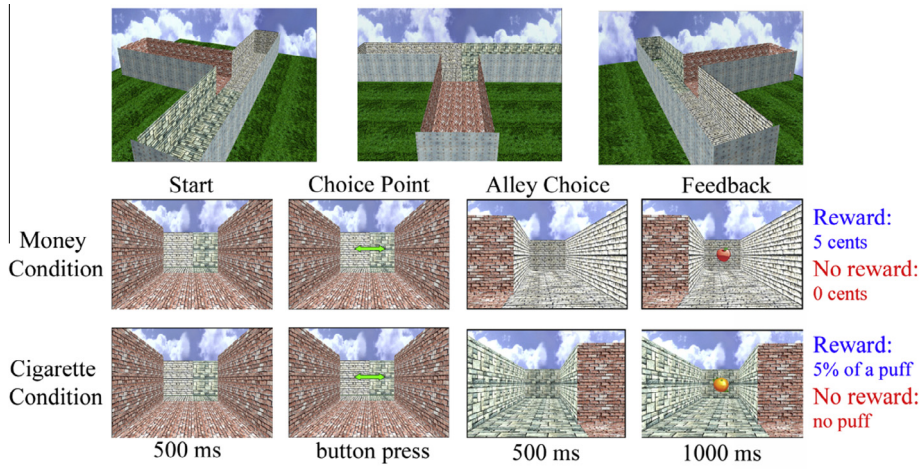

Fig. 1. Virtual T-Maze. Top panels: Areal views of the T-maze provided to subjects at the beginning of each block of trials. Middle and bottom panels: From left to right, participants' views of the start image, followed by the choice image with double arrow indicating left or right alley choice, followed by the image of the selected alley, and finally the feedback stimulus. Middle panels depict an example trial for the money condition, and bottom panels depict an example trial for the cigarette condition. Feedback was presented in the form of virtual fruit (apples, oranges, pineapples and lemons). In the money condition, the feedback stood for either 5 cents or no money. In the cigarette condition, the feedback stood for either 5% of 1 3 s-long puff of a cigarette or no puff.

Table 1
Sample characteristics (n = 24).

	ND		SD		$F(df) = t$, p-value, η^2
	M	SE	*M*	SE	
Sample (*N*)	n = 12		n = 12		
Sex (male/female)	4/8		7/5		
Age	21.5	0.7	21.1	0.7	$F(1,22) = 0.176$, $p = 0.679$, $\eta^2 = 0.01$
GCR	17.8	1.0	48.3	2.0	$F(1,22) = 153.8$, $p < .001$, $\eta^2 = 0.88$
Smoking behavior					
Nicotine dependence	10.4	0.8	11.7	0.6	$F(1,22) = 1.32$, $p = 0.262$, $\eta^2 = 0.06$
Cigarettes per day	4.4	1.0	3.4	0.7	$F(1,22) = 0.72$, $p = 0.404$, $\eta^2 = 0.03$
Age of onset	16.6	0.8	14.3	0.7	$F(1,22) = 3.47$, $p = 0.076$, $\eta^2 = 0.14$
Years smoking	4.9	0.7	6.8	1.2	$F(1,22) = 0.44$, $p = 0.646$, $\eta^2 = 0.02$
CO levels					
Time 1	9.4	2.5	10.1	2.5	$F(1,22) = 0.04$, $p = 0.837$, $\eta^2 = 0.00$
Time 2	5.7	1.5	8.6	1.5	$F(1,22) = 1.49$, $p = 0.234$, $\eta^2 = 0.06$
Time 3	8.9	1.3	12.4	1.6	$F(1,22) = 2.66$, $p = 0.12$, $\eta^2 = 0.11$
TCQ					
Time 1	4.0	0.3	4.1	0.2	$F(1,22) = 0.187$, $p = 0.670$, $\eta^2 = 0.01$
Time 2	4.3	0.2	4.5	0.3	$F(1,22) = 0.22$, $p = 0.645$, $\eta^2 = 0.01$

Numbers indicate means and standard errors of the mean, except for Sample, which indicates sample size (*N*), and Sex, which indicates participant number (male/female).

scalp distributions were inspected to confirm the spatial distribution of the component.

2.3.3. Statistical analysis

A 3-factor mixed-design ANOVA with Condition (cigarette, money) as a within-subject factor, and Order (money first, cigarette first) and Group (SD, ND) as between-subject factors were conducted for reward positivity amplitude and latency. The Benjamini–Hochberg procedure was used to correct for multiple testing in all post hoc analyses.

3. Results

3.1. Smoking behavior

Apart from GCR scores, the two groups did not differ on any of the measured indices and reported comparable levels of smoking behavior (Table 1). Note that this means that even though the SD individuals tended to abuse a range of addictive drugs, they smoked about as frequently as did the non-dependent population. Overall, paired sample t-tests indicated that the CO levels at the start of Session 2 following an overnight period of abstinence (M = 6.0 ppm, SEM = 0.7) were significantly lower than the levels during Session 1 (M = 9.8 ppm, SEM = 1.6), $t(23) = 2.3$, $p < .05$, and the levels at the end of Session 2 following the consumption of a cigarette (M = 10.7 ppm, SEM = 1.1), $t(23) = -6.7$, $p < .001$; the difference between the latter two CO levels was not statistically significant ($p > .05$). Conversely, participant TCQ scores for Session 2 (M = 4.4, SEM = 0.19) were significantly larger than the scores for Session 1 (M = 4.04, SEM = 0.19), $t(42) = -2.6$, $p < .01$. Together, these results suggest that smoking abstinence prior to the experiment increased participants' subjective levels of cigarette craving (Fig. 2).

3.2. ERP results

Because the reward positivity to drug-related feedback stimuli has not yet been investigated, we first examined whether or not

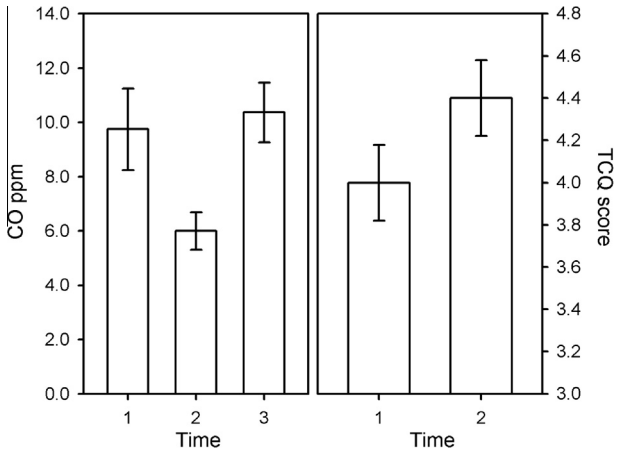

Fig. 2. Smoking index. Left panel: CO levels taken at Time 1 (session 1), Time 2 (start of session 2) and Time 3 (immediately after cigarette consumption). Right panel: Tobacco Craving Questionnaire (TCQ) at Time 1 (session 1) and Time 2 (session 2).

cigarette-related rewards elicit this ERP component as a precondition for the remainder of the analyses. Fig. 3 presents stimulus-locked grand averages for both feedback conditions at channel FCz. Consistent with previous research, the reward positivity elicited in the money condition was clearly evident in the difference wave peaking 288 ms after feedback onset (Fig. 3A, solid lines), and was significantly different from zero, $t(23) = -10.51$, $p < 0.001$, 95% confidence interval = [−4.9 μV, −3.29 μV]. The reward positivity elicited in the cigarette condition peaked 297 ms after feedback onset (Fig. 3A, dashed lines) and was also significantly different from zero, $t(23) = -14.02$, $p < 0.001$, 95% confidence interval = [−5.74 μV, −4.27 μV]. Further, as shown in Fig. 3b, the frontal–central distributions for both conditions are consistent with the identification of this ERP component as the reward positivity (Miltner et al., 1997), indicating that cigarette-related feedback is capable of eliciting the reward positivity in smokers.

Next, a 3-factor mixed-design ANOVA on reward positivity amplitude with Condition (cigarette, money) as a within-subject factor, and Order (money first, cigarette first) and Group (SD, ND) as between-subject factors revealed a main effect of Condition $F(1, 20) = 4.56$, $p < .05$, $\eta^2 = 0.19$, indicating that the reward positivity in the cigarette condition ($M = -5.01$ μV, $SEM = 0.35$) was larger than the reward positivity in the money condition ($M = -4.1$ μV, $SEM = 0.33$) (Fig. 3A). Further, the 3-factor ANOVA also revealed an interaction between Group and Order, $F(1, 20) = 9.32$, $p < .01$, $\eta^2 = 0.32$ (Fig. 4). Post-hoc analysis revealed that for subjects who engaged in the money condition first, the amplitude of the reward positivity (collapsed across money and cigarette conditions) was smaller for the SD group ($n = 6$, $M = -3.3$ μV, $SEM = 0.53$) compared to the ND group ($n = 6$, $M = -5.2$ μV, $SEM = 0.53$) participants, $t(10) = -2.17$, $p < .05$, $d = 1.37$ (Fig. 4, left panel). By contrast, for the subjects who engaged in the cigarette condition first, the

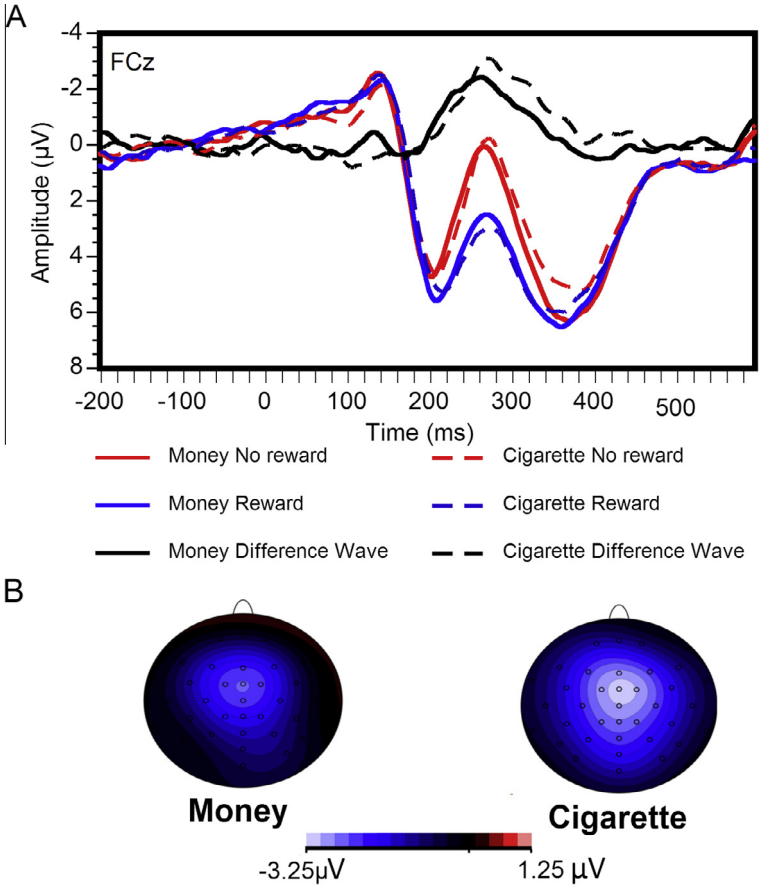

Fig. 3. Main effect of condition on the reward positivity. (A) ERPs elicited by reward feedback (blue), no reward feedback (red) and associated difference wave (black) for the money condition (solid lines) and cigarette condition (dashed line), averaged across groups. The reward positivity is assessed as the amplitude of the difference wave. Data associated with channel FCz. Negative is plotted up by convention. (B) Scalp voltage maps associated with the peak value of the reward positivity for the money condition (left) and cigarette condition (right) averaged across groups. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

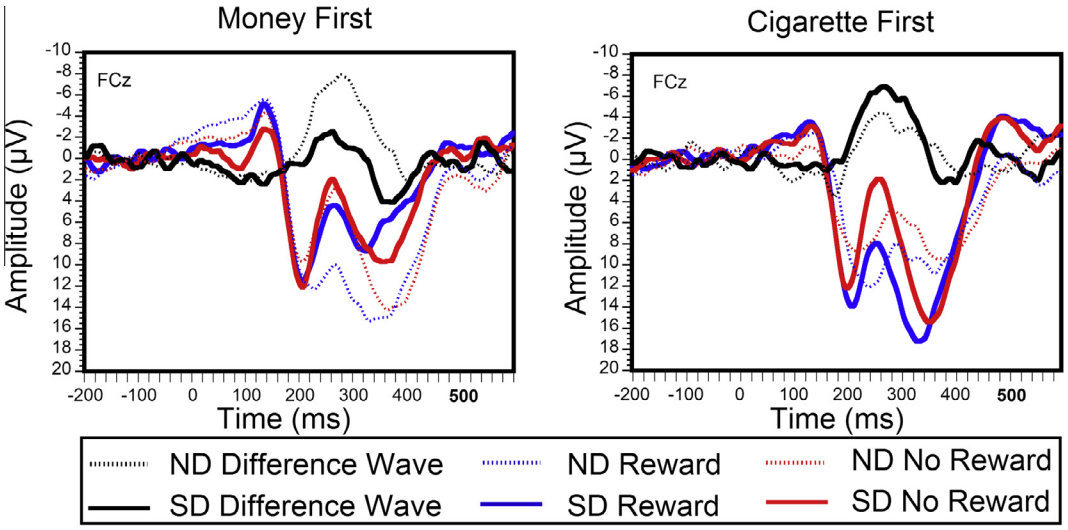

Fig. 4. Interaction effects on reward positivity amplitude. ERPs elicited by reward feedback (blue), no reward feedback (red) and associated reward positivity (black) for the Money First group (left) and Cigarette First group (right), averaged across money and cigarette conditions, separately for the non-dependent (ND, dotted lines) and substance dependent (SD, solid lines) participants. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

amplitude of the reward positivity (collapsed across money and cigarette conditions) was larger for the SD group ($n = 6$, $M = -5.5$ μV, $SEM = 0.53$) compared to the ND group ($n = 6$, $M = -4.1$ μV, $SEM = 0.53$), $t(10) = -2.18$, $p < .05$, $d = 1.38$. No main effects of Group [$p > .05$, $\eta^2 = 0.01$] and Order [$p > .05$, $\eta 2 = 0.05$], nor interactions between Condition and Group [$p > .05$, $\eta^2 = 0.03$], and Condition, Group, and Order [$p > .05$, $\eta^2 = 0.02$], were detected. Further, no main effects nor interactions were observed for the latency of the reward positivity ($p > .05$).

We had expected that the reward positivity would be reduced to monetary rewards in the SD population relative to the ND population irrespective of condition order. For this reason, we were surprised to find the interaction between Group and Order instead of the predicted interaction between Group and Condition. We therefore explored the possibility that the money-first condition – which most closely aligns with the task design used in our previous studies (Baker et al., 2011) – would replicate our finding that the reward positivity to monetary feedback is reduced in SD but not ND individuals. Indeed, for those subjects who performed the money condition first, the reward positivity to monetary rewards was truncated in the SD group ($M = -2.5$ μV, $SEM = 0.42$) relative to the ND group ($M = -4.4$ μV, $SEM = 0.6$), $t(10) = -2.34$, $p < 0.05$, $d = 1.48$, replicating the finding, yet no group differences in the reward positivity amplitude were observed for cigarette rewards in that condition ($p > .05$, $d = .88$), nor for the group comparisons for monetary ($p > .05$, $d = .73$) and cigarette rewards ($p > .05$, $d = 1.04$) in the cigarette-first condition. Further, general sample characteristic (Table 1) were similar across groups based on Order ($p > .05$), and groups based on Dependence and Order ($p > .05$).

4. Discussion

Numerous studies have focused on the contributions of subcortical brain structures to substance dependence, especially the ventral striatum, which is commonly thought to learn and implement relatively simple stimulus–response associations (Yin and Knowlton, 2006; Redish et al., 2008). Yet complex and flexible behaviors directed toward drug acquisition are not easily explainable in terms of the simple stimulus–response habits said to be mediated by the striatum (Robinson and Berridge, 2008)[1]. Instead, the striatum appears to contribute to the production of stereotypical behaviors involved in drug consumption (Yin and Knowlton, 2006). Although a few neuroimaging studies have reported ACC hyperactivation to drug-related rewards and hypoactivation to natural rewards (Peoples, 2002; Goldstein et al., 2007), the contribution of ACC to substance dependence is less well understood. As described above, the ACC appears to be involved in the flexible deployment of extended, goal-directed behaviors (Holroyd and McClure, 2015; Holroyd and Yeung, 2012), and our previous observation of reduced reward positivity amplitude – which is said to reflect phasic modulation of ACC activity by dopamine RPE signals (Holroyd and Coles, 2002) – in SD individuals suggests abnormal control over these behaviors (Baker et al., 2011, 2015a). This interpretation raises the question of whether the reduced reward positivity reflects impaired reward valuation per se or a specific devaluation of "normal" rewards relative to drug-related rewards in SD individuals.

To our knowledge, this study is the first to examine electrophysiological measures of reward processing using both drug (nicotine) and non-drug (money) related rewards in the same individuals. Our first goal was to replicate the standard reward positivity effect using cigarette related rewards in the T-maze task. Our results clearly demonstrate that reward positivity amplitude was modulated by cigarette reward versus no-reward feedback in the virtual T-maze task. Further, drug-related rewards (nicotine) elicited a relatively larger reward positivity than non-drug-related rewards (money) in abstinent smokers, suggesting that in a state of drug craving, the ACC assigned a larger reward value to goal-directed behaviors that are drug-related.

We were particularly interested in whether feedback stimuli indicating small monetary rewards would elicit an attenuated reward positivity in SD compared to ND individuals, as previously demonstrated (Baker et al., 2011, 2015a), and further, whether drug-related rewards would normalize this impairment. Evidence for this possibility would have been revealed by an interaction between Group and Condition in the 3-way ANOVA. Surprisingly, however, the ANOVA instead yielded an interaction between Group

[1] Robinson and Berridge (2008) have commented that 'addicts in the real world are not stimulus response automatons; they are, if nothing else, quite resourceful' (Robinson and Berridge, 2008, pp. 1338).

and Order. In particular, for the individuals who participated in the money condition first, the reward positivity (averaged across the money and cigarette conditions) was attenuated in SD individuals compared to ND individuals, but for those who participated in the cigarette condition first, the reward positivity amplitude was larger in SD individuals compared to ND individuals. Closer inspection revealed that for the participants who performed the money condition first, the reward positivity was larger for the ND compared to SD individuals, replicating our previous findings (Baker et al., 2011, 2015a). Further, consistent with our predictions, this difference was normalized by cigarette rewards for the participants who performed the cigarette condition first. What we did not predict is that this pattern of differences would continue into the second block of trials for each group, as suggested by the absence of an interaction between Group and Condition: for the people who did the money condition first, the reward positivity continued to be relatively smaller to the cigarette rewards for the SD individuals relative to the ND individuals, and for the people who did the cigarette condition first, and the reward positivity continued to be as large to the money rewards for the SD individuals as for the ND individuals.

This result seems to suggest that the initial category of feedback "primed" the response of the ACC to the alternative feedback type on subsequent trials, and that SD and ND individuals responded differently to the initial priming. Note that the cigarettes were consumed only after both conditions were completed, so the priming effect was not due to an acute effect of nicotine consumption. Although any interpretation of this result is necessarily post hoc, a recent computational model of ACC function suggests the following possibility (Holroyd and McClure, 2015). On this account, ACC allocates control over extended task performance according to a feedback control loop: ACC increases control when the received rewards are less than the average reward value for the task, and releases control when received rewards are more than the average reward value for the task. Under the assumption that the cigarette and money conditions were represented by the control system as different episodes of the same task, then the SD individuals who received the monetary rewards during the second block of trials may have evaluated those rewards as "worse" than the average value for the preceding cigarette rewards, precipitating increased control over task performance during the second block and a concomitantly large reward positivity to the money rewards. By contrast, for those SD individuals who received the money rewards first, a low task reward value associated with the first block of trials may have resulted in reduced task motivation to engage in the second block of trials and, as a consequence, a relatively smaller reward positivity to cigarette rewards. It is also conceivable that the SD individuals failed to update the feedback stimulus category (fruit) following the first condition, i.e., that they continued to encode the fruit as representing monetary rewards and non-rewards rather than drug rewards and non-rewards.

Still another possibility is that the effect of Group and Order is a chance finding, reflecting an unbalanced mix of participants in the Money-first vs. Cigarette-first groups. Although we cannot rule out this possibility, the money-first condition constitutes the second replication (and the third time showing) that small monetary rewards elicit a reduced reward positivity in SD vs. ND individuals (Baker et al., 2011, 2015a). This reduction occurred despite normal amplitude of other ERP components such as the P300 (Baker et al., 2011, 2015a), suggesting equal attention to task demands (Yeung et al., 2005). Further, general sample characteristic (Table 1) were similar across groups based on Order, and groups based on Dependence and Order, which argues against the possibility that our results stem from an imbalanced grouping of participants. The large reward positivity observed here to the SD participants in the cigarette condition therefore appears contrary to an established, replicable finding. It is also worth noting that the absence of an interaction between Group and Condition could be due to the low statistic power given the small sample size. Thus, we recommend that future investigations replicate and extend this result by adopting a larger and more refined within-subjects design for presenting a variety of "normal" (e.g. food, social, monetary) rewards relative to drug-related rewards.

A further limitation of the study was that the sample consisted entirely of undergraduate students recruited from the University of Victoria who may not be representative of the general substance dependent population. Future studies should replicate and extend these findings with a wider sample of the general population (e.g. Baker et al., 2015b), clinical samples of individuals seeking treatment (e.g. Baker et al., 2013), people who abuse specific drugs or drug types (such as cocaine; Parvaz et al., 2015, but see Baker and Holroyd, 2015), and people with behavioral addictions (such as addiction to pornography, the internet, or gambling).

These observations elucidate an important yet under-investigated role of the ACC in assigning reward value to the maladaptive, goal-directed behaviors characteristic of SD. That the reward positivity is also abnormal in several other psychiatric disorders (Proudfit, 2015) suggests that ACC may implement a crucial neurocognitive function that cuts across traditional diagnostic categories (Insel et al., 2010; Cuthbert and Insel, 2013; Cuthbert and Insel, 2010; Holroyd and Umemoto, 2015). In particular, the reward positivity is well-positioned to serve as a biomarker (Proudfit, 2015) or intermediate phenotype (Baker, et al., 2015a) of reward-related psychopathology associated with abnormalities of the mesocorticolimbic reward and cognitive control systems. We recently identified a specific molecular pathway by which the DRD4-521 genotype alters ACC electrophysiology and thereby predicts the level of problematic substance use in undergraduate students (Baker et al., 2015a), supporting the proposal that ACC function can serve as an intermediate phenotype for individual differences in substance dependence. Gene studies have also revealed substantial heritability of the reward positivity, suggesting that it can serve as an intermediate phenotype for psychopathologies associated with abnormal regulation of behavior (Anokhin et al., 2008; Olvet and Hajcak, 2009; Olvet and Hajcak, 2008). Taken together, a close examination of the role of ACC in controlling complex behaviors should advance clinical and therapeutic research in these domains.

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