Cigarette craving is associated with blunted reward processing in nicotine-dependent smokers

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ABSTRACT

Background: Dysfunctional reward processing leading to the undervaluation of non-drug rewards is hypothesized to play a crucial role in nicotine dependence. However, it is unclear if blunted reward responsivity and the desire to use nicotine are directly linked after a brief period of abstinence. Such an association would suggest that individuals with reduced reward responsivity may be at increased risk to experience nicotine craving.

Methods: Reward function was evaluated with a probabilistic reward task (PRT), which measures reward responsivity to monetary incentives. To identify whether smoking status influenced reward function, PRT performance was compared between non-depressed, nicotine-dependent smokers and non-smokers. Within smokers, correlations were conducted to determine if blunted reward responsivity on the PRT was associated with increased nicotine craving. Time since last nicotine exposure was standardized to 4 h for all smokers.

Results: Smokers and non-smokers did not differ in reward responsivity on the PRT. However, within smokers, a significant negative correlation was found between reward responsivity and intensity of nicotine craving.

Conclusions: The current findings show that, among smokers, the intensity of nicotine craving is linked to lower sensitivity to non-drug rewards. This finding is in line with prior theories that suggest reward dysfunction in some clinical populations (e.g., depressive disorders, schizophrenia) may facilitate nicotine use. The current study expands on such theories by indicating that sub-clinical variations in reward function are related to motivation for nicotine use. Identifying smokers who show blunted sensitivity to non-drug-rewards may help guide treatments aimed at mitigating the motivation to smoke.

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1. Introduction

Dysfunctional reward processing, which commonly manifests as the overvaluation of drug-related rewards and undervaluation of other non-drug reinforcers (e.g., food, sex, money), plays a key role in substance abuse (Blum et al., 2000; Garavan et al., 2000; Goldstein et al., 2007; Kalivas and Goldstein, 2005; Versace et al., 2012). This is true for nicotine-dependent individuals, who demonstrate reduced reward reactivity to non-drug reinforcers during nicotine withdrawal (Al-Adawi and Powell, 1997; Powell et al., 2002a,b. 2004). Conversely, when present, nicotine enhances the reward value of non-drug stimuli leading tobacco smokers to experience relatively heightened pleasure or potentiated reward responsiveness (Barr et al., 2008; Dawkins et al., 2006; Kenny and Markou, 2006).

Nicotine’s ability to enhance reward function suggests that the propensity to smoke may be higher in those with blunted hedonic capacity (Audrain-McGovern et al., 2012), implying that nicotine may ameliorate an underlying disruption in reward function (Cardenas et al., 2002; Janes et al., 2015). This hypothesis would explain the high prevalence of nicotine dependence in psychiatric disorders that are characterized by blunted hedonic capacity such as major depressive disorder (Glassman et al., 1990) and schizophrenia (de Leon et al., 1995; de Leon and Diaz, 2005). Such
a hypothesis may extend to a more general population without clinically significant anhedonia, suggesting that individuals with sub-clinical disruption in reward function may have increased motivation to smoke.

Although reduced reward function is thought to play a role in maintaining nicotine dependence (Bühler et al., 2010; Koob and Le Moal, 2001; Volkow et al., 2010), it is still unclear if blunted reward processing is directly linked to an increased desire to smoke. Preliminary support for this notion comes from evidence showing that anhedonia – a blunting of hedonic capacity – is associated with greater nicotine craving when individuals abstain from smoking (Cook et al., 2004; Leventhal et al., 2009). However, not all smokers report anhedonic symptoms, making it unclear whether sub-clinical reductions in reward function are linked to nicotine craving in the general smoking population. Such an association would suggest that maintenance of smoking in individuals with no overt reward-related pathology may be driven by a mechanism in which subtle reductions in reward sensitivity are linked to increased nicotine craving.

Furthermore, it is unknown if the relationship between craving and reward function is present shortly after smoking. Symptoms of withdrawal and craving emerge after short periods of abstinence, likely contributing to the maintenance of daily smoking behaviors that often involve brief delays between self-administration (Brown et al., 2013; Harrison et al., 2006; Gross et al., 1997). It is unlikely that pharmacological withdrawal alone drives the desire to smoke during this time, as nicotine continues to occupy most of the brain's high affinity β2 nAChRs for up to 5 h following a single smoking episode (Staley et al., 2006). Further, temporal onset of subjective craving is not impacted by acute nicotine administration as compared to placebo (Brown et al., 2013; Gross et al., 1997). Understanding the factors that may relate to nicotine craving within this window, such as blunted reward responsivity, may help elucidate the emergence of craving during brief abstinence.

To clarify the relationship between craving and reward function after a brief period of abstinence, we evaluated nicotine-dependent smokers using a probabilistic reward task (PRT) 4 h after smoking. This task has been used extensively to evaluate individual's ability to modify behavior as a function of monetary (non-drug) reinforcement (AhnAllen et al., 2012; Janes et al., 2015; Pechtel et al., 2013; Pizzagalli et al., 2005, 2008, 2009; Santesso et al., 2008) and is sensitive enough to detect not only disruptions in reward processing (Pizzagalli et al., 2005, 2008), but nicotine-related perturbations in reward sensitivity (Barr et al., 2008; Janes et al., 2015; Pergadia et al., 2014).

In this context, PRT task performance was first compared between briefly abstinent nicotine-dependent smokers and healthy non-smokers to determine whether there were differences in reward responsivity between groups. Next, the relationship between reward responsivity and nicotine craving was evaluated in smokers by correlating PRT task performance with subjective craving as measured by the Questionnaire for Smoking Urges (QSU; Cox et al., 2001), which is a standard assessment of nicotine craving. We hypothesized that smokers with relatively lower non-drug reward responsivity would report more intense nicotine craving, highlighting a link between blunted reward sensitivity and maintenance of nicotine use. Exclusionary criteria for all participants included current medical illness, pregnancy, recent drug/alcohol use (confirmed by a QuickTox11 Panel Drug Test Card, Branam Medical Corporation, Irvine California; Alco-Sensor IV, Intoximeters Inc., St. Louis, MO), current drug or alcohol dependence (other than nicotine for the smoker cohort), current major depressive disorder, and current or lifetime diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or psychotic disorders not otherwise specified. Although two participants in the smoking group reported experiencing a single past depressive episode, none of the data collected from these participants were statistical outliers when compared to the rest of the smoking group. Thus, these individuals were included in all analyses.

Smokers reported smoking an average of 14.2 cigarettes per day in the past 6 months (SD = 4.00), reported an average pack-year (cigarettes per day x years of smoking) of 7.14 (SD = 4.75), and had an average expired air carbon monoxide (CO) of 21.57 ppm (SD = 12.78) at screening. Non-smokers were age- and sex-matched to the smoking participants, and reported smoking <5 cigarettes in their lifetime. The Institutional Review Board at McLean Hospital approved all study procedures. Participants provided written informed consent and were compensated for their participation.

2.2. Assessment of tobacco use and craving

To standardize the time since the last cigarette was smoked, all smokers smoked one of their own cigarettes after the informed consent procedure. Non-smokers did not smoke a cigarette. Approximately 4h after smoking and ~30 min prior to completing the probabilistic reward task, subjective tobacco craving was measured with the 10-item brief version of the QSU (Cox et al., 2001).

2.3. Beck Depression Inventory-II and positive and negative affect schedule

Although all participants were excluded for current depression (as confirmed by the SCID), depressive symptom severity across the past 2 weeks was evaluated using the Beck Depression Inventory-II (BDI; Beck et al., 1996) at the beginning of the study visit. The BDI also provided an index of self-reported anhedonia, which has previously been associated with PRT performance (Pizzagalli et al., 2005). The anhedonic subscale (RDI_anhedonia) consists of BDI-II items evaluating loss of pleasure (item 4), loss of interest (item 12), and loss of interest in sex (item 21); Joiner et al., 2003.

The state version of the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) was administered immediately after smoking and again ~4h later when the QSU was completed. This allowed for the evaluation of any possible changes in mood state across this 4-h window, as a reduction in positive affect over significantly longer delays in smoking is associated with anhedonia and cigarette craving (Cook et al., 2004). To obtain change in mood state scores, initial PANAS scores were subtracted from the score obtained after ~4 h of abstinence.

2.4. Probabilistic reward task (PRT)

Participants performed a computerized PRT to assess responsiveness to non-nicotine related rewards. The task was adapted from Tripp and Alsop (1999) by Pizzagalli et al. (2005) to objectively assess reward responsivity by identifying an individual's propensity to modify behavior as a function of recent reinforcement history. The task has been described in detail elsewhere (see Pizzagalli et al., 2005) and validated in multiple, independent samples (e.g., Barr et al., 2008; Janes et al., 2015; Pizzagalli et al., 2008, 2009; Pergadia et al., 2014).

Each trial of the task consisted of the presentation of a fixation cross, followed by a mouth-less cartoon face. Following a delay of 500 ms, either a short mouth (11.5 mm) or a long mouth (13 mm) was presented for 100 ms. Participants were asked to identify which type of mouth was presented via computer key-strike. Long and short mouths were presented equally often in a pseudorandomized sequence. Some, but not all, correct answers were followed by monetary reward feedback (e.g., “Correct!! You won 5 cents”) with an asymmetrical reinforcement ratio such that correct identification of the one mouth (the rich stimulus) was rewarded three times (n = 30) more often than the correct identification of the other mouth (the lean stimulus) (n = 10). Participants completed one of three versions of the task. Versions were identical on all aspects but reward value. Reward values were 5 cents, 20 cents, or 1 dollar. Influence of reward value was assessed prior to all statistical analyses. The task consisted of two blocks of 100 trials each, with a short (30s) break in between blocks. Following established procedures (see Pizzagalli et al., 2005), response bias was calculated for each block of 100 trials. Higher response bias values suggest greater responsivity to the monetary reward. All smokers performed the PRT approximately 4h after smoking a cigarette.

2.4.1. PRT calculations and quality assessment

Following prior procedures (e.g., Pizzagalli et al., 2005, 2008) four, a priori criteria were used to assess the validity of the PRT task data: (1) trials with reaction times <150 ms or >2500 ms were considered invalid and blocks with >20% invalid trials were removed, (2) trials with reaction times (following natural log transformation) falling outside the range of mean ± 3 SD were considered outliers and participants with greater than 20 outliers over the course of both blocks were removed, (3) blocks with less than 50% (chance) response accuracy were removed, and (4) blocks with a reward ratio (rich:lean) less than 0.8 were removed.
than 2.5 were removed. Participants were only included in the analysis if both the first and second blocks were considered valid. In total, 39 smoking participants completed the PRT and 9 were excluded because they did not meet the above criteria. Five participants did not meet criterion 1, 7 did not meet criterion 2, 1 did not meet criterion 3, and 7 did not meet criterion 4. Non-smoking participants were extracted as age and education matched controls from an existing database. Signal detection analysis (Macmillan and Creelman, 2005) was used to calculate response bias (i.e., preference for more frequently rewarded stimulus) and discriminability (i.e., the ability to distinguish between stimuli types). Response bias and discriminability were calculated as follows:

Response bias: \( \frac{RB_{Correct} + LEAN_{Correct}}{RB_{Correct} + LEAN_{Correct}} \)

Discriminability: \( \log d = \frac{1}{2} \log \left( \frac{RB_{Correct} + LEAN_{Correct}}{RB_{Correct} + LEAN_{Correct}} \right) \)

In addition, 0.5 was added to each cell in the calculation matrix to allow computation in cases of no mistakes. Change in response bias from block 1 to block 2 (\( \Delta RB \)) was calculated by subtracting the average response bias in block 1 from the average response bias in block 2. This value was used to capture reward learning over the course of the task. Change in discriminability (\( \Delta d \)) was calculated in the same manner.

2.5. Analyses

2.5.1. Between group analysis. Before any analyses were conducted, BDIanhedonia scores were log-transformed to achieve normality. Independent samples t-tests were used to evaluate group differences (smoker vs. non-smoker) on age, BDI scores, and BDIanhedonia scores.

As data from different versions of the PRT task were used in this analysis, a repeated measures ANOVA was used to rule out the effect of reward type on change in response bias. This analysis was run with the between-subjects factor Reward Type (5 cents, 20 cents, 1 dollar) and the within-subjects factor Block (block 1, block 2). Next, to examine if there were group differences in response bias acquisition, a second repeated measures ANOVA was run with the between-subjects factor Group (smokers, non-smokers) and the within-subjects factor Block (block 1, block 2). Finally, we examined if there were any differences between the groups in overall task difficulty (i.e., discriminability), using a third repeated measures ANOVA with the between-subjects factor Group (smokers, non-smokers) and the within-subjects factor Block (block 1, block 2).

2.5.2. Within smoker analysis. To evaluate the relationship between tobacco craving and reward responsivity in smokers, a two-tailed Pearson’s correlation was performed between QSU scores and \( \Delta RB \). As a follow up to examine any influence of smoking habits on our main analysis of interest, two-tailed correlations were conducted between QSU, \( \Delta RB \), and BDIanhedonia, change in positive affect, change in negative affect, expired CO, pack-year, number of cigarettes smoked per day and number of cigarettes smoked before the study. Partial correlations were performed controlling for variables with a significant relationship with QSU score or \( \Delta RB \).

3. Results

3.1. Group differences

Smokers and non-smokers did not differ in age (\( t(53) = -1.41, p = .17 \)). The groups were significantly different on BDI scores such that the smoking group (\( M = 3.53, SD = 3.45 \)) scored significantly higher than the non-smoking group (\( M = 0.50, SD = 1.29 \); \( t (52) = -4.44, p = .001 \)). Similarly, the smoking group scored significantly higher on the BDIanhedonia (\( M = 0.37, SD = 0.67 \)) compared to the non-smoking group (\( M = 0.00, SD = 0.00 \); \( t (52) = -3.00, p = .001 \)). However, a correlation revealed no significant relationships between BDI and \( \Delta RB \), or between BDIanhedonia and \( \Delta RB \) among all participants. Critically, the mean scores on the BDI (3.53 and .5 for smokers and non-smokers respectively) were not clinically significant, as a score of 14 is the threshold for mild depression. Similarly the magnitudes of the mean differences between groups (3.03 and 0.37 for BDI and BDIanhedonia, respectively) also were not clinically significant.

To determine if there were differences in performance on the different versions of the task, a repeated measures ANOVA was run on response bias (block 1 and block 2) with reward type as the independent variable. No significant main effects or interactions involving reward type emerged (all \( p > .05 \)), suggesting that the type of reward given in the task did not impact rate of reward learning (consistent with the notion that the asymmetry of the reinforcement schedule is the most important variable responsible for the induction of response bias). Next, we examined response bias across two blocks of the task with smoking group as the independent variable. A repeated measures ANOVA revealed no significant main effect of smoking group (\( F (1, 53) = 19, p = .066, \eta^2 = .004 \), Fig. 1) or interactions between smoking group and block. Finally, we examined if there were any differences between the groups in overall task difficulty (i.e., discriminability). No main effects or interactions emerged involving discriminability (all \( p > .05 \)).

3.2. Within smoker correlations

In line with our a priori hypothesis, \( \Delta RB \) and QSU were negatively correlated (\( r = -.40, p = .030 \), two tailed, Fig. 2). There were no significant relationships between QSU and any of the other variables of interest (BDIanhedonia, change in positive affect, change in negative affect, expired CO, pack-year, number of cigarettes smoked per day, and number of cigarettes smoked before the study; all \( p > .05 \); see Table 1). Further, there were no significant relationships between \( \Delta RB \) and BDIanhedonia, change in positive affect, change in negative affect, pack-year, number of cigarettes smoked per day, and number of cigarettes smoked before the study at the level of \( p < .05 \) (see Table 1). However, there was a significant negative relationship between \( \Delta RB \) and expired CO (\( r = -.47, p = .008 \)) at the \( p < .05 \) level and a negative relationship between \( \Delta RB \) and cigarettes before the study and \( \Delta RB \) and cigarettes per day at a more liberal level of \( p < .01 \). When controlling for expired CO, the association between \( \Delta RB \) and QSU fell below significance, but remained at a trend level with a comparable correlation coefficient.
Table 1

<table>
<thead>
<tr>
<th>ΔRB</th>
<th>QSU</th>
<th>r</th>
<th>p</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDIanhedonia</td>
<td>.038</td>
<td>.844</td>
<td>-.199</td>
<td>.292</td>
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</tr>
<tr>
<td>Positive affect change</td>
<td>.063</td>
<td>.663</td>
<td>.129</td>
<td>.496</td>
<td></td>
</tr>
<tr>
<td>Negative affect change</td>
<td>-.092</td>
<td>.628</td>
<td>.205</td>
<td>.277</td>
<td></td>
</tr>
<tr>
<td>Expired CO on arrival</td>
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<td>.007**</td>
<td>.275</td>
<td>.141</td>
<td></td>
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<tr>
<td>Pack-year</td>
<td>-.150</td>
<td>.430</td>
<td>.110</td>
<td>.563</td>
<td></td>
</tr>
<tr>
<td>Cigarettes/day</td>
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<td>.061</td>
<td>.019</td>
<td>.919</td>
<td></td>
</tr>
<tr>
<td>Cigarettes before study</td>
<td>-.310</td>
<td>.095</td>
<td>.242</td>
<td>.198</td>
<td></td>
</tr>
</tbody>
</table>

Note: All r values represent two-tailed Pearson’s correlation coefficients. * p < .05. ** p < .001.

\[(r = -.32, p = .096)\]. When controlling for cigarettes before the study, the association between ΔRB and QSU fell below significance, but remained at a trend level with a comparable correlation coefficient \[(r = -.35, p = .064)\]. When controlling for cigarettes per day, the relationship between ΔRB and QSU remained significant \[(r = -.42, p = .025)\].

4. Discussion

It is well documented that disrupted reward function and subjective drug craving play a central role in addiction (Blum et al., 2000; Buhler et al., 2010; Garavan et al., 2000; Goldstein et al., 2007; Kalivas and Goldstein, 2005; Koob and Le Moal, 2001; Versace et al., 2012; Volkow et al., 2010). The current findings link these two concepts by showing an association between reduced reward function, as assessed by an objective behavioral measure of reward responsivity, and greater subjective report of cigarette craving. Furthermore, although extended nicotine withdrawal is associated with reduced reward responsivity (Al-Adawi and Powell, 1997; Powell et al., 2002a,b, 2004) and acute administration of nicotine has been shown to enhance reward sensitivity (Barr et al., 2008; Dawkins et al., 2006; Kenny and Markou, 2004), the current results reveal no group differences in reward function between smokers and non-smokers. This lack of group difference indicates that any reduction in reward responsivity associated with withdrawal was not detectable within ~4 h of smoking. This suggests that nicotine-related enhancements in reward responsivity may still be present after a short period of abstinence.

The present finding extends the current literature in two important ways. First, by showing a link between blunted reward responsivity and nicotine craving in smokers who lack a current overt pathological disruption in reward processing, and secondly by showing that this link exists even following recent smoking. The present report builds upon the work of Cook et al. (2004) and Leventhal et al. (2009) who found that individuals having traits associated with reduced reward function, such as anhedonic symptoms, were more likely to experience heightened craving following nicotine withdrawal. Not only did our cohort of smokers not report clinically relevant depressive or anhedonic symptoms as measured by the BDI, there were no associations between any slight variability in responses on these measures and craving or reward responsivity. Furthermore, changes in positive affect over the 4-h period since participants last smoked did not explain the relationship between blunted reward responsivity and increased cigarette craving. Regardless, smokers with the lowest reward responsivity measured by the PRT reported the greatest tobacco craving. This finding is relevant as it indicates that behavioral measures may be more sensitive at defining variation in reward function than self-report and that such variation is related to the motivation to smoke.

Further, we found a significant negative association between reward responsivity and craving following recent smoking. This point is important given that others have linked self-report measures of reward disruption with craving measures assessed following 12–24 h of nicotine withdrawal (Cook et al., 2004; Leventhal et al., 2009), implying that such an association would only become apparent following a significant period of abstinence. The current findings indicate that a link between reward responsivity and craving is detectable following just 4 h of abstinence. Although participants may not be experiencing high levels of pharmacological withdrawal after 4 h (Staley et al., 2006), they are likely experiencing varying degrees of craving, as the urge to smoke emerges as early as 1 h post cessation (Gross et al., 1997; Schuh and Stitzer, 1995; Tiffany and Drobes, 1991). This finding suggests that variation in reward responsivity is not only related to tobacco craving during lengthy abstinence, but also may influence daily smoking patterns, which involve shorter delays between nicotine administration.

A number of associations between response bias and self-report measures of daily smoking behavior emerged in these analyses. Response bias was correlated with expired CO at the time of arrival, and modestly correlated with self-reported cigarettes smoked per day and cigarettes smoked before the study. However, only expired CO and cigarettes smoked before the study impacted the relationship between response bias and craving. Although expired CO is commonly used as a measure of smoking recency, CO levels also increase proportionally with the number of cigarettes smoked in a short period of time (Henningfield et al., 1980), suggesting that expired CO upon arrival and cigarettes before the study may be capturing the same variation in ad lib smoking behavior. Furthermore, the time between smoking and reward responsivity was held constant, so the association between expired CO at the time of arrival and responsivity cannot be explained by smoking recency.

Importantly, higher CO levels are associated with several aspects of smoking topography including increased puff volume, greater number of puffs, longer puff duration (Frederiksen and Martin, 1979), and longer time to finish a cigarette (Ahijevych and Gillespie, 1997). It is possible that individuals with blunted reward responsivity have higher CO levels upon arrival because they smoke in such a way that increases nicotine absorption. Thus, in our sample, reward responsivity may be not be related to the amount that an individual is smoking in terms of cigarettes per day but the way they smoke, which enhances nicotine absorption.

One explanation as to why craving and reduced reward function are linked is that they may share a common neural substrate. One candidate is the mesocorticolimbic reward pathway, which is critically involved in both reward processing (Morris et al., 2004) and craving (Due et al., 2002; Garavan et al., 2000; McClernon et al., 2005, 2009; Volkow et al., 2003, 2010). In fact, alcohol craving is associated with blunted brain reward activity during the anticipation of non-drug related rewards (Wrase et al., 2007). If craving and reward processing share a common brain substrate, it is likely that treatments ameliorating one symptom will also impact the other. Although the exact mechanisms of action are unknown, preliminary support for this has been shown in a rodents model of nicotine dependence, whereby the smoking cessation aid bupropion enhances reward sensitivity (Cryan et al., 2003), and in humans this same medication reduces reported nicotine craving (Duran et al., 2002).

There are a number of limitations to this study that merit discussion. First, the relatively modest sample size may have impacted our ability to find differences between the smoking and non-smoking...
group. Thus, a larger group will be necessary to confidently generalize these findings. Second, we are unable to determine whether individual differences in nicotine bioavailability influenced subjective craving or reward function as measured by the PRT. We attempted to account for such effects in several ways, such as standardizing the time since participants last smoked and evaluating the effect of daily smoking behavior on reward and craving. However, other factors such as genetic variation can impact nicotine metabolism (Tyndale and Sellers, 2002), which may have influence on our measures of interest. Future research should focus more directly on whether such factors play a role in individual variation in reward function and cigarette craving, which would clarify the mechanism for this link. Despite this limitation our findings still show a clear association between reward function and craving. Critically, this association was found in smokers without currently elevated levels of anhedonia.

In sum, while past research has identified that overt levels of anhedonia are associated with desire for nicotine (Cook et al., 2004; Leventhal et al., 2009), we have identified a relationship between a behavioral measure of reward responsibility and nicotine craving. Furthermore, this association can be detected recently after smoking, indicating that a lengthy withdrawal period is not necessary to detect associations between reward sensitivity and craving. This finding may impact clinical care, as transitioning behavioral measures of reward function into the clinic may be useful in identifying individuals who may be prone to more intense cravings, and may as such, experience greater difficulty quitting smoking.

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Contributors

Ms. Peetchata and Dr. Janes conceptualized the study. Dr. Pizzagalli provided the signal detection task and critical insight into the analysis and interpretation of results. Ms. Farmer was integral in data collection. Ms. Peetchata, Dr. Janes, and Dr. Whitten analyzed the data. Ms. Peetchata and Dr. Janes drafted the manuscript. Ms. Peetchata consolidated edits from coauthors. All authors approved the final manuscript.

Conflict of interest

Over the past two years, Dr. Pizzagalli has received honoraria/consulting fees from Otsuka America Pharmaceutical, Pfizer, and Servier for activities unrelated to this project. All other authors declare no conflicts of interest.

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