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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.

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

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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.

2. Material and methods

2.1. Participants

Fifty-five individuals, 30 nicotine-dependent smokers and 25 non-smokers, completed study procedures at McLean Hospital. All smokers met DSM-IV criteria for current nicotine dependence, which was verified by the Fagerström Test for Nicotine Dependence (FTND; Fagerström, 1978) with an average score of 5.93 (SD = 1.26). All participants were administered the Structured Clinical Interview for DSM Disorders I (SCID-I; First et al., 2002) to identify current and past psychopathology.

Exclusionary criteria for all participants included current medical illness, pregnancy, recent drug/alcohol use (confirmed by a QuickTox11 Panel Drug Test Card, Branan 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 × 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 4 h 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 ($BDI_{anhedonia}$) 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 ~4 h later when the QSU and the PRT were administered. 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 responsivity 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 reinforcer 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 (30 s) 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 4 h 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 55% (chance) response accuracy were removed, and (4) blocks with a reward ratio (rich:lean) less