The Synergistic Effect of Cigarette Demand and Delay Discounting on Nicotine Dependence among Treatment-Seeking Smokers

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Abstract

From a behavioral economics standpoint, tobacco addiction can be conceptualized as a reinforcer pathology deriving from high cigarette demand and elevated delay discounting (DD) rates. The primary aim of this study was to assess the interactive effects of cigarette demand and DD on nicotine dependence (ND) and cigarette consumption among a sample of treatment-seeking smokers. Participants were 277 smokers (68.9% women) who completed the 19-item version of the Cigarette Purchase Task (CPT), a computerized version of the DD task and the Fagerström Test for Nicotine Dependence (FTND). To assess cigarette consumption, participants were also asked about their mean number of cigarettes smoked per day (CPD). Hierarchical multiple regressions were conducted to assess the interactive effects of demand indices and DD on ND and CPD. The area under the curve (AUC) for both demand and DD was used to explore the interactive effect of the two variables. Results showed that the interaction between cigarette demand and DD was significantly related to ND severity ($p < .05$), but not to cigarette consumption. This is the first study showing that the synergistic effect of cigarette demand and DD better accounts for ND in treatment-seeking smokers than the two isolated constructs. It also supports the utility of AUC as a proxy for cigarette demand providing methodological convergence with other behavioral economic domains, such as DD.

Keywords: Cigarette demand; Delay discounting; Reinforcer pathology; Behavioral economics; Nicotine dependence.

Public significance statement: This study highlights the importance of considering both cigarette demand and delay discounting when characterizing nicotine dependence.

Effective treatment approaches that reduce one of these two facets of reinforcer pathology may also have the potential to alter the other.

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There are no known conflicts of interest, including financial, personal, or other relationships with other organizations or pharmaceutical or biomedical companies.

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The content and data that appear in this study have not been previously disseminated elsewhere.

The Synergistic Effect of Cigarette Demand and Delay Discounting on Nicotine Dependence among Treatment-Seeking Smokers

From a behavioral economics perspective, nicotine dependence (ND) can be conceptualized as a reinforcer pathology derived from the effects of persistently high cigarette demand and excessive preference for immediate rewards (Bickel, Johnson, Koffarnus, MacKillop, & Murphy, 2014; Bickel, Snider, Quisenberry, & Stein, 2017). Cigarette demand refers to the examination of nicotine consumption under escalating conditions of financial or response cost and shows the amount of money or effort that a person is willing to make to obtain cigarettes (MacKillop & Tidey, 2011). On the other hand, delay discounting (DD) refers to the observation that the value of a delayed reward is discounted (considered to be worth less) compared to the value of an immediate reward (Bickel & Marsch, 2001), and is commonly used as an index of impulsive decision making (Owens, Amlung, Beach, Sweet, & MacKillop, 2017; Rung & Madden, 2018). Smokers with high demand value cigarettes substantially more than other rewards and are less sensitive to changes in cigarette price (MacKillop et al., 2012; Murphy, MacKillop, Tidey, Brazil, & Colby, 2011; Secades-Villa, Weidberg, Gonzalez-Roz, Reed, & Fernandez-Hermida, 2017). Cigarette demand is usually assessed by examining performance in a cigarette purchase task (CPT), which assesses hypothetical cigarette purchases at escalating prices (MacKillop et al., 2008). The other behavioral economic domain, DD, is usually explored through the assessment of preferences between smaller immediate rewards (commonly money) and larger delayed rewards. Smokers have consistently been shown to discount more by delay when compared to non-dependent controls (Bialaszek, Marcowski, & Cox, 2017; García-

Rodríguez, Secades-Villa, Weidberg, & Yoon, 2013) and DD correlates with severity of nicotine dependence (Amlung, Vedelago, Acker, Balodis, & MacKillop, 2017).

Although both drug demand and excessive DD are two well-established characteristics of reinforcer pathology (Bickel, Jarmolowicz, Mueller, & Gatchalian, 2011; Bickel, et al., 2014), to our knowledge, no study to date has primarily assessed the potential interactive effects of cigarette demand and DD on ND and cigarette consumption. As both constructs have proven to be solid markers in the development and progression of substance use disorders, the examination of their interplay would help to identify distinct phenotypes of reinforcer pathology (Bickel, et al., 2014). This may allow cigarette smokers to receive specific treatment components based on the particular functional phenotype they have.

The only studies assessing the relationship between the two behavioral constructs have been conducted with heterogeneous samples of alcohol drinkers, smokers with and without psychopathology, and cannabis users, and their results are mainly inconclusive. While MacKillop et al. (2010) found a significant association between DD and intensity of alcohol demand in heavy drinkers, two other studies found no correlation between alcohol demand and DD among college students (Amlung et al., 2013; Teeters & Murphy, 2015). Nevertheless, relationships between alcohol demand and discounting were secondary findings based solely on bivariate analyses, and not the research focus of the studies. When considering smokers with and without psychopathology, Farris, Aston, Abrantes, and Zvolensky, (2017) demonstrated the existence of significant correlations between several demand indices and DD for rewards of large magnitude, while Mackillop and Tidey (2011) did the same, but only when DD for rewards of small magnitude were considered. Notwithstanding these findings, assessing correlations between demand and DD is not enough for exploring their interplay within the reinforcer pathology model. In this regard, only two studies have primarily addressed the question of whether the combination of cannabis demand and DD predicted both the frequency of cannabis use and number of dependence symptoms (Aston, Metrik, Amlung, Kahler, & MacKillop, 2016; Strickland, Lile, & Stoops, 2017), showing that demand and DD appear to be more independently than synergistically related to cannabis use and dependence. These studies were conducted with non-treatment seeking marijuana users, and given that motivation for achieving abstinence from drug use can influence drug demand (Mackillop et al., 2016), this limits their potential for generalizing to drug dependent individuals who are seeking treatment.

We sought to address these knowledge gaps by assessing the interactive effects of cigarette demand and DD on ND and cigarette consumption among treatment-seeking smokers.

Method

Participants and procedure

The participants were 277 treatment seeking smokers who participated in two randomized clinical trials (RCTs) related to the treatment of ND among smokers with (NCT03163056) (n = 127) and without depressive symptomatology (Secades-Villa, García-Rodríguez, López-Núñez, Alonso-Pérez, & Fernández-Hermida, 2014) (n = 150). Inclusion criteria for all participants were: being at least 18 years old, meeting the diagnostic criteria for ND according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV-TR) (American Psychiatric Association, 2000) assessed by the structured Clinical Interview for DSM-IV (SCID-I), and having smoked

10 or more cigarettes per day for the prior 12 months. Participants were excluded if they were currently participating in other smoking cessation treatment, if they had a diagnosis of a current severe psychiatric disorder, or if they misused or were dependent on a substance other than nicotine. An additional inclusion criterion for the first study was meeting criteria for current unipolar major depressive disorder (MDD) according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev; DSM-IV-TR) and/or scoring ≥14 points on the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996). Baseline characteristics of the participants are presented in Table 1.

Please insert Table 1 here

This study was conducted at the clinical unit of the Addictive Behaviors Research Group (University of Oviedo, Spain). The Institutional Review Board of the University of Oviedo approved the study protocol and informed consent was obtained from all participants.

Instruments and variables

Participants completed an ad hoc questionnaire in a single baseline session to gather data on sociodemographic characteristics (age, gender, marital status, income, and years of education). ND was explored through the Fagerström Test for Nicotine Dependence (FTDN) (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). Cigarette consumption was assessed by asking participants about their mean number of cigarettes smoked per day (CPD). All participants were asked to provide breath carbon monoxide (CO) and urine samples to yield objective verification of current cigarette use. Breath samples of CO were obtained using a piCO Smokerlyzer (Bedfont Scientific Ltd., Rochester, UK). A BS-120 chemistry analyzer (Shenzhen Mindray Bio-medical

Electronics Co. Ltd., Shenzhen, P. R. China) was also used to determine urine cotinine levels through a homogeneous enzyme immunoassay system. Smoking status was defined as presenting a CO level of ≥ 4 ppm (ppm) and a urinary cotinine sample of ≥ 80 nanograms per milliliter (ng/ml).

The Beck Depression Inventory (BDI-II) (Beck, et al., 1996) was used to assess the depressive symptoms. Scores range from 0 to 63. A score less than 13 represents minimal depression, 14 to 19 indicates mild depression, 20 to 28 suggests moderate depression, and scores above 29 are indicative of severe depression.

Participants completed a hypothetical CPT to assess cigarette demand. The instructional set has been reported elsewhere (see Secades-Villa, Pericot-Valverde, & Weidberg, 2016). In brief, participants were asked to indicate how many cigarettes they would purchase at 19 prices [€0 (free), €0.01/$0.012 , €0.02/$0.025, €0.05/$0.062, €0.10/$0.12, €0.25/$0.31, €0.50/$0.62, €1/$1.24, €2/$2.48, €3/$3.72, €4/$4.96, €5/$6.20, €10/$12.40, €20/$24.81, €50/$62.03, €100/$124.06, €250/$310.16, €500/$620.31, €1,000/$1,240.62]. All prices were presented in escalating order.

A computerized DD task was presented to the participants. They were trained in how to interact with the DD program and informed that they would not obtain any of the monetary amounts presented, but they were asked to respond as if their selections were real. Participants were presented with a choice between €1,000 ($1,240.62) after a fixed delay, versus various amounts of money ranging from €5 ($6.20) to €955 ($1,184.70) available immediately using an adjusting-amounts procedure (Holt, Green, & Myerson, 2012). Based on the participant's response, the value of the immediate monetary option ranged from €5 to €1,000 in €5 increments and was adjusted via a titrating procedure. This procedure yielded an indifference point, in which the value the immediate amount and the delayed €1,000 are deemed equal. Seven escalating delay values were presented, ranging from 1 day to 25 years.

Data analysis

Five metrics obtained from the CPT were analyzed, including (1) intensity: cigarette consumption at zero cost; (2) O_{max}: maximum amount of money allocated to cigarettes; (3) P_{max}: price at the maximum expenditure; (4) breakpoint: cost at which consumption is suppressed to zero; (5) elasticity: sensitivity of cigarette consumption to increase in cost. Elasticity was estimated by fitting each participant's informed consumption using the exponentiated model proposed by Koffarnus, Franck, Stein, and Bickel (2015):

$$Q = Q_0 \times 10^{k(e^{-\alpha Q_0 C}-1)} \qquad (1)$$

where Q = consumption at given price; Q_0 = consumption at zero price, k = range of dependent variable (number of cigarettes), C = price, and α = elasticity of demand. As in previous studies using the CPT (Farris et al., 2017), the suitable k value used was determined by subtracting the log10-transformed average consumption at the highest price (€1000/$1,240.62) from the log10-transformed average consumption at the lowest price (€0.01/$0.012). Thus, a fixed value of k = 3.02 was collapsed for all participants. An R^2 value was generated through nonlinear regression to estimate goodness of data fit. CPT values were examined in order to identify misunderstanding or low effort during the task performance (i.e., persistent task inattention or low motivation when fulfilling the task). Following the criteria of > 2 contradictions at ascending prices (that is, > 2 increases in cigarette purchases as the price rises; Acker and MacKillop, 2013), CPT data from one participant were removed from the analyses.

In addition, CPT indices were observed with a view to detecting outliers and distribution abnormalities. Following the recommendation of Tabachnick and Fidell (2006), demand indices were standardized and compared to a critical value of Z = ± 3.29. Twenty-two outliers were identified and recoded as the highest non-outlying value by adding one ten thousandth place (0.0001) to elasticity values and one unit (1.00) to the remaining demand indices. A procedure described by Hursh and Winger (1995) was used to normalize the demand curve. This procedure sets cigarette consumption at the lowest price (highest dose at the lowest fixed ratio) to the same normalized value of 100. Normalized dose (q) was calculated as $q = 100/B$, where B = consumption at the lowest price. Normalized dose was then used to generate values for normalized price (P) as $P = FR/q$, where FR is the response requirement, namely the increase in cigarette price. Normalized dose was also used to generate values for normalized consumption (Q) as $Q = Rq$, where R refers to reported consumption.

The area under the normalized demand curve was based on normalized demand curves computed using the following formula proposed by Hursh and Winger (1995): area = FR_{max}/q x qR_{max}. As the q values cancel, the formula is reduced to: area under the normalized demand curve = FR_{max} x R_{max} = O_{max} (response level at P_{max} or maximum output of responding). This procedure is suitable to calculate the area under the normalized demand curve as it is consistent with the peak response level maintained by the drug (i.e., Omax) (Hursh and Winger, 1995). Higher CPT-AUC values mean greater tobacco demand.

Indifference points were examined in order to identify non-systematic DD data following the criteria specified by Johnson and Bickel (2008). All DD data fitted such criteria. Indifference points from each DD task were also summarized using the AUC proposed by Myerson, Green, & Warusawitharana (2001) as an atheoretical discounting measure that avoids assumptions of any specific discounting model to characterize demand.

Pearson´s correlations were used to assess the relationship between cigarette demand metrics, DD and ND and CPD. Two hierarchical multiple regressions were used to examine the impact of the interaction between CPT-AUC and DD-AUC on ND and on CPD. CPT-AUC was included in this model as a single proxy of tobacco demand to avoid methodological problems in the study of interactions among DD and cigarette demand, and to support convergence with prior research (Aston, et al., 2016). To interpret the potential interactive effects between cigarette demand and DD, DD-AUC values were reversed in the models. Income, gender, and RCT condition were entered into an initial block as covariates to determine the unique contribution of all CPT metrics and DD-AUC. Analyses were conducted using GraphPad Prism 6.0 (La Jolla, California) and SPSS (version 24, SPSS Inc., Chicago IL, USA).

Results

Self-reported cigarette demand

The cigarette demand curve was prototypical (see Figure 1). The exponentiated demand equation showed an excellent fit to the overall demand data (mean R^2 = .97, median R^2 = .98, interquartile range: .96 - .99). Participants purchased a mean of 21 cigarettes up to a price of €0.10 each. When the price reached €0.25 per cigarette, which is the closest cost to the actual price participants pay for their own cigarettes, they self-reported purchasing 19 cigarettes. The majority of participants (79%) still purchased an average of 6.34 cigarettes (SD 6.37) if each cigarette were to cost €2 each. The first price at which 55.4% of the sample reported they would not purchase any cigarettes was €5. Figure 2 depicts the expenditure curve, showing an increase in cigarette expenses as the price per cigarette rises.

Please insert Figures 1 and 2 here

Association between cigarette demand, DD, ND and CPD

Bivariate correlations among cigarette demand metrics, DD-AUC, ND, and CPD are shown in Table 2. All demand indices were significantly intercorrelated. The majority of the associations were positive, with the exception of elasticity, which was negatively correlated with the remaining variables (including CPT-AUC, ND, and CPD). According to the guidelines established by Cohen (1988), the strongest associations were found between O_{max} and CPT-AUC, breakpoint and P_{max} and CPT-AUC and P_{max}. CPT-AUC was significantly correlated with all demand indices, showing large correlations with breakpoint, O_{max} and $P_{max.}$ DD-AUC was positively associated with breakpoint, O_{max} and P_{max} and CPT-AUC, although the strength of these correlations was small. FTND and CPD were significantly associated with all cigarette demand variables including CPT-AUC.

Please insert Table 2 here

Interactive effects of cigarette demand and DD on ND and CPD

Table 3 provides results of the regression models of cigarette demand and DD over ND (model 1) and CPD (model 2). Among the covariates, RCT condition showed significance in model 1, which means that participating in the RCT of smokers with depressive symptoms was related to higher ND. Gender was also a significant covariate in model 2, showing that being a male was associated with a higher number of CPD.

When CPT-AUC and DD-AUC were considered in models 1 and 2, their main effects were not significant. However, the interaction between the variables was significantly related to ND severity, but not to CPD.

Please insert Table 3 here

Discussion

This study had the novel aim of exploring the association of cigarette demand and DD with ND severity and CPD among treatment-seeking smokers. Results showed that (1) the interaction between cigarette demand and DD better accounted for ND than the two isolated facets of reinforcer pathology, but this effect was not found for CPD; and (2) DD-AUC was positively associated with breakpoint, Omax, Pmax and CPT-AUC.

A novel and interesting finding of this study is the interactive influence of cigarette demand and DD on ND severity. The advantage of using the same parameter (AUC) to assess both cigarette demand and DD adds solid support to the notion that these two behavioral economic domains display synergistic roles in contributing to ND severity. Thus, smokers who are nicotine dependent show the two essential components of the reinforcer pathology paradigm (high cigarette demand and DD), which jointly increase the risk for showing elevated ND. This result contrasts with previous studies conducted among cannabis users that did not detect an interaction between marijuana demand and DD on different cannabis-use variables (Aston, et al., 2016; Strickland, et al., 2017). However, these studies were conducted with marijuana users who were not seeking treatment. In fact, in the study from Aston et al. (2016), only 14% of the sample reported fulfilling the criteria for cannabis dependence and Strickland et al. (2017) did not biochemically verify cannabis use. Thus, their findings cannot be generalized to cannabis dependent individuals who are motivated to seek treatment, making them barely comparable with treatment seeking smokers who are nicotine dependent, like the ones used in the present study.

Although the interaction between cigarette demand and DD was related to ND severity, it was not associated with CPD. While ND is frequently assessed, it is rarely dissociated from cigarette consumption. However, this study supports the notion that ND and CPD tap into different aspects of the smoking phenomenon; while the CPD item only measures differences in nicotine exposure (Sweitzer, Donny, Dierker, Flory, & Manuck, 2008), the instrument used to assess ND (i.e., FTND) also contains items indexing impaired control (Hughes et al., 2004) and nicotine withdrawal (DiFranza, 2013). The fact that ND was explored using a more complex instrument could account for the interactive influence of cigarette demand and DD on this construct, but not on CPD.

We found small, but unexpected, positive correlations between DD-AUC values and several demand metrics (breakpoint, Omax, Pmax and CPT-AUC). This means that those smokers with lower impulsive decision-making showed higher cigarette demand. The study of the associations between DD and drug demand has provided mixed results, with some studies finding significant associations between both behavioral economic domains (MacKillop et al., 2010) while others showed no relationship between the two constructs (Aston et al., 2016; Teeters & Murphy, 2015). Nevertheless, the fact that these studies assessed DD and drug demand using samples of individuals dependent on different substances and with different drug use severity might account for these discrepant results.

Some limitations of this research merit mention. First, its cross-sectional design precludes the assumption of an etiological association between ND and the two behavioral economic domains, cigarette demand, and DD. Second, demand and DD were assessed using hypothetical behavioral tasks. Nonetheless, there is a close correspondence between hypothetical and real rewards in both discounting (Lagorio & Madden, 2005) and demand procedures (Amlung & MacKillop, 2015). Third, participants in this study were obtained from two different RCTs, although the effect of the RCT condition was controlled in the statistical analyses. Despite these shortcomings, strengths of this study include a large sample of treatment seeking smokers and the use of AUC as a common proxy for assessing both cigarette demand and DD.

Overall, our results support the notion that high cigarette demand and excessive DD rates jointly enhance the reinforcer pathology that characterizes ND. This has a pragmatic value for the development of effective treatment approaches that minimize the risk for relapse. Previous studies have shown interventions that are able to reduce either DD (Bickel, Yi, Landes, Hill, & Baxter, 2011; Houben, Wiers, & Jansen, 2011; Weidberg, Landes, García-Rodríguez, Yoon, & Secades - Villa, 2015) or cigarette demand (Weidberg, Vallejo-Seco, Gonzalez-Roz, Garcia-Perez, & Secades-Villa, 2018). In this regard, novel interventions such as Episodic Future Thinking have shown to reduce these two facets of reinforcement pathology (DD and cigarette demand) simultaneouly (Stein, Tegge, Turner, & Bickel, 2018), but there is a need for more studies that replicate this finding. Finally, the association between cigarette demand and DD found in this study highlights the importance of using transdiagnostic behavioral measures (i.e., AUC) in future research to provide methodological convergence across different domains of reinforcer pathology.

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