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Effects of Negative Affect, Urge to Smoke, and Working Memory Performance (n-back) on Nicotine Dependence

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Abstract

Background—Three key domains including negative emotionality, incentive salience, and executive function form the core functional elements of addictive behaviors. Variables related to these broader domains have been studied extensively in relation to one another; however, no studies to date, have examined models including variables from all three domains, in relation to nicotine dependence.

Method—Smokers (N=117), 65.8% female, 78% white, mean age of 44.4 (SD=10.8), enrolled in a smoking cessation program completed measures of negative affect (a component of negative emotionality), urge to smoke (incentive salience), and working memory (WM; a core executive function), during a baseline assessment period prior to initiating treatment.

Results—Negative affect was associated with greater urge to smoke, and this elevated urge to smoke was associated with higher levels of nicotine dependence. Further, a significant moderated mediation indicated that WM moderated the relationship between increased urge to smoke and nicotine dependence. For those with low to average WM, urge to smoke was significantly related to nicotine dependence; however, for those with higher WM (+1SD), urge to smoke stemming from negative affect was not associated with nicotine dependence.

Conclusions—To our knowledge, this is the first reported relationship between negative affect, urge to smoke, WM, and nicotine dependence. Although preliminary, results indicate that WM may moderate the relationship between urge to smoke associated with negative affect and nicotine

dependence. Treatments targeting WM may be particularly useful for individuals with average to low WM who experience urge to smoke related to negative affect.

INTRODUCTION

A body of evidence indicates that three key domains including negative emotionality, incentive salience, and executive function form the core functional components of addictive disorders¹. Many studies have examined the influence of these domains on tobacco use in isolation (e.g. effects of negative mood²³, urge to smoke⁴, or working memory performance⁵ on tobacco use), or in relation to one another (e.g. effects of negative mood on urge to smoke⁶). However, a gap exists in the literature regarding how variables from all three of these domains interact within individuals in relation to nicotine dependence. Understanding how variables representing these domains are interrelated among smokers may help inform the design of prospective studies and development of novel smoking cessation treatments.

Negative affect is a core component of negative emotionality, and plays an important role in smoking maintenance²⁴⁷, at least in part, by increasing urge to smoke^{68–10}. At the initiation of smoking cessation, individuals who experience higher negative affect display a steeper rate of relapse throughout the first year⁴. Urge/craving (referred to herein as urge)¹¹ to smoke, a measure tied to incentive salience¹²¹³, is among the strongest and most reliable predictors of dependence and smoking lapse^{14–16}. Both general urge, measured in the absence of any specific tobacco related cue, and cue-induced urge are strongly associated with nicotine dependence, even when controlling for factors such as years of smoking and cigarettes smoked per day¹⁴. Prospective studies have demonstrated that urge to smoke predicts subsequent lapse¹⁵¹⁷. Urge peaks during initial abstinence and declines quickly as time passes in sustained abstinence¹⁵¹⁷. However, initial urges must be tolerated in order to maintain abstinence, creating acute conflict between the drive to smoke and the resources one has available to abstain¹⁵.

Working memory (WM), an executive function responsible for information storage, updating, and resistance to distraction^{18–20}, has been shown to be involved in the initiation, maintenance, and relapse stages of tobacco dependence^{21–27}. Most notably, deficits in WM performance and associated brain regions predict time to smoking relapse²⁴²⁶, possibly by moderating the effect of urge to smoke²⁷. This important moderation can be understood within the context of dual process models of addiction. Dual process models view vulnerability to addiction as the relative balance between automatic impulses (i.e. urges) and regulatory control processes orchestrated through the interplay of multiple executive functions^{28–30}. WM is a key cognitive process underlying the executive control component of dual process models²⁸³¹. Thus, according to dual process models of addiction, WM may be important in overcoming urges to smoke, and in this way – particularly important for individuals high in negative affect given that these individuals tend to experience stronger urges.

Variables related to these domains have been studied extensively in relation to one another; however, to our knowledge, no studies have examined models including variables from all three of these domains in relation to nicotine dependence. The aim of the current study was

to examine relationships among negative affect, urge to smoke, and WM performance in relation to nicotine dependence, in a sample of treatment-seeking smokers just prior to a quit attempt. Given the past body of literature cited, we hypothesized that negative affect would be associated with increased urge to smoke, and that higher urge to smoke would in turn be related to increased dependence to nicotine. Furthermore, we hypothesized that this relationship would be moderated by WM performance, in line with dual process models of addiction. Lastly, we aimed to examine how individual performance indices of the N-back (correct response rate, d prime, and false alarm rate) relate to the key addiction related domains included in the current study.

METHOD

Participants

Participants were 117 treatment seeking smokers who enrolled in a smoking cessation program ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02086149) # [NCT02086149](https://clinicaltrials.gov/ct2/show/study/NCT02086149)). The Butler Hospital IRB approved all procedures. The inclusion criteria were that participants (a) were between 18–65 years of age, (b) smoked 10 cigarettes/day, and (c) reported elevated depressive symptoms (Center for Epidemiological Studies – Depression Symptoms, CES-D 6). As required for the parent study, CES-D for all participants was equal to or greater than 6; ensuring that all participants experienced at least some degree of negative emotionality.

Exclusion criteria included: (a) any current DSM-IV Axis I psychiatric disorder except Major Depressive Disorder or Nicotine Dependence Disorder, (b) any recent initiation or change in pharmacotherapies for depression, (c) current use of any treatment for smoking cessation or (d) active engagement in an aerobic exercise program (more than 90 minutes per week).

The sample was predominately female (65.8%), with an average age of 44.4 years ($SD=10.8$; range: 23–63); .9% self-identified as Asian, 4.3% Black, 77.8% White, 6.8% Multi-racial, 2.6% as other, 6.4% as Hispanic. Participants demonstrating any current DSM-IV Axis I psychiatric disorder except Major Depressive Disorder were excluded; 15.1% of the sample met criteria for Current Major Depressive Disorder, and mean CESD for the sample was 16.66 ($SD=11.8$). On average, participants smoked 19.2 ($SD=7.3$) cigarettes per day had been smoking regularly for 24.0 ($SD=10.0$) years. Descriptive statistics for variables including negative affect, urge to smoke, working memory, and nicotine dependence are listed in Table 1.

Procedure

Participants attended baseline sessions in which they completed measures of negative affect, urge to smoke, nicotine dependence, and a neuropsychological task assessing WM performance. The present study focuses on the baseline assessment period because smoking behavior prior to arriving at baseline sessions was ad libitum, resulting in levels of urge to smoke, affect, and cognitive performance that should approximate typical daily experience. Data collection for the larger prospective study is currently ongoing ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02086149) # [NCT02086149](https://clinicaltrials.gov/ct2/show/study/NCT02086149)).

Measures

Fagerstrom Test for Cigarette Dependence (FTCD)³²: The FTCD is a widely used and well-validated measure of nicotine dependence severity. FTCD scores of 0–2 indicate very low dependence, 3–4 indicate low dependence, 5 indicates medium dependence, 6–7 indicate high dependence, and 8–10 indicate very high dependence³³.

Positive and Negative Affect Schedule (PANAS)³⁴: The PANAS was used to measure negative affect over the past week. The negative affect scale is a 10-item subscale. The total score is computed by averaging responses to all items. The subscale has evidenced excellent reliability and convergent validity with relevant correlates³⁴.

Minnesota Nicotine Withdrawal Scale (MNWS)¹¹³⁵.—Urge/craving (urge) was measured with the urge subscale of the MNWS. This scale consists of items assessing urge/craving to smoke measured with a Likert scale ranging from 0 (no symptoms) to 4 (severe symptoms). Additionally, one item assessing motivation to quit was assessed within the MNWS and included as a covariate in all models. Study subjects were asked to rate their symptoms according to how they felt or what they noticed over the past 24 hours.

Smoking History Questionnaire and Demographics: this measure assessed years of smoking, cigarettes smoked per day, participant sex, and age.

Working Memory (n-back).—The computerized n-back is a well-established index of WM performance³⁶, which requires flexible updating capabilities. The n-back assessment included a visuospatial 2-back task requiring maintenance and updating of two locations. The primary outcome measure utilized in the current study was correct response rate on the 2-back trial (hits/ (hits + misses)). The maximum number of correct responses was 30. In order to provide a comprehensive report of N-back performance we also examined additional outcome performance indices including d' prime (d'), and the false alarm rate³⁷. d' provides information regarding how well a participant is able to discriminate targets from non-targets, and has been shown to measure a domain of executive working memory that is separate from other executive functions such as learning and memory, motor speed, or executive flexibility³⁷. d' is calculated using the formula: $d' = Z_{Hit} - Z_{FA}$ (Macmillan & Creelman, 1990; ³⁷), where Hit represents (hits/ (hits + misses)), and FA represents (false alarms/(false alarms + correct rejections))³⁷. Lastly, we examined the false alarm rate, which has been proposed as an index of impulsivity³⁷, within the moderated-mediation model.

Analytic Strategy

Mediation and moderated mediation analysis using bootstrapping with replacement³⁸ was utilized in order to estimate the indirect effects of negative affect on tobacco dependence via urge to smoke, and to examine the moderating effects of WM performance. Bias-corrected bootstrapping with 1000 bootstrap samples was conducted using the SPSS PROCESS macro; this technique was chosen for its ability to maximize the power to detect mediation and allowance of non-normality^{38–40}. This modeling technique estimates simultaneous regression analyses and generates confidence intervals that correct for bias in estimating the indirect effects. The PROCESS macro only estimates unstandardized regression coefficients.

An indirect effect is determined to be statistically significant if the confidence interval does not contain zero.

First, we examined an initial mediation model where the indirect effects of negative affect (X) on nicotine dependence (Y) were mediated by urge to smoke (M) (Model 1). Next, we added working memory performance (2-back correct response rate) (V) as a moderator of the relationship between urge to smoke and dependence, thus creating a moderated mediation model (Model 2). We also tested Model 2 with d' (Model 2a), and False Alarm Rate (Model 2b), as (V) the moderator of the relationship between urge to smoke and dependence. Age, sex, and reported motivation to quit were selected *a priori* as covariates based on the previous literature and included in all models.

RESULTS

Descriptive and Correlations

Mean scores and zero-order correlations for key variables can be found in Table 1. As predicted, negative affect was significantly correlated with urge to smoke, and urge to smoke was significantly correlated with nicotine dependence. WM performance, in isolation, was not significantly correlated with any variables.

Mediation and Moderated Mediation

As depicted in Figure 1, we observed significant indirect effects of negative affect on nicotine dependence through urge to smoke. Individuals reporting higher negative affect in the week prior endorsed greater urge to smoke, which was in turn associated with higher score on the Fagerstrom Test for Nicotine dependence (model 1: indirect effect = .029, 95% CI [.0087 - .0592], $p < .05$). Next, we added WM performance to the model, thus creating a moderated mediation model, and observed that WM moderated the relationship between urge to smoke and nicotine dependence (model 2: moderated mediation index = -0.069, 95% CI [-.1163 -0.0076], $p < .05$). Greater urge to smoke was associated with nicotine dependence in individuals with average (sample mean) or below average (1SD below mean) WM performance. However, for individuals with high WM performance (1SD above mean), the relationship between urge to smoke and nicotine dependence was not significant. Similarly, a significant finding with the same pattern of results was observed when correct response rate was replaced with d' (Model 2a; moderated mediation index = -0.0108, 95% CI [-.0222 -0.0031], $p < .05$). No significant moderated mediation was observed in the model (Model 2b) examining False Alarm Rate as the moderator.

DISCUSSION

This study provides preliminary information regarding three key functional domains in addiction, as they relate to nicotine dependence. In line with previous research⁶¹⁴, significant linear relationships were observed between negative affect and urge to smoke, and urge to smoke and nicotine dependence. This study expands the literature by demonstrating significant indirect effects of negative affect on nicotine dependence through urge to smoke, and furthermore, that the relationship between urge to smoke and tobacco dependence is moderated by working memory (WM) performance. Thus, it appears that all

three domains play an important role in maintaining dependence to nicotine, at least for individuals with average or lower than average WM performance. Moreover, these results highlight the potential for interventions that target executive functions to disrupt the relationship between commonly present individual factors (negative emotionality) and nicotine dependence, and may be particularly relevant in treatment development for patient-populations who exhibit these factors in addition to high smoking rates (e.g. ⁴¹). The current finding that WM moderates urge to smoke is in line with a previous study demonstrating a similar effect on urge to smoke following alcohol administration²⁷; the current study provides new information by demonstrating this effect in the absence of alcohol consumption and in the context of negative affect. Interestingly, negative affect was not correlated with nicotine dependence in this sample; this may reflect that the effect of negative affect on nicotine dependence is largely contingent upon craving, or that the current sample was restricted to those with at least modestly elevated negative emotionality – thus limiting variance that might account for the direct relationship observed in other samples. More generally, this finding aligns with dual process models of addiction^{30,42}, by demonstrating that one's vulnerability to dependence reflects the balance between the executive control system (represented by WM) and urge to consume the substance.

In order to provide a comprehensive examination of performance on the N-back task, we tested additional indices including d' and the false alarm rate (FA), within the context of the moderated mediation model. d' (d prime), a performance index shown to have high specificity to WM and strong concurrent validity with other measures of WM³⁷, was observed to moderate the relationship between urge to smoke and nicotine dependence in a pattern similar to the primary working memory index examined (n-back correct response rate). Conversely, FA, a performance measure which has been proposed to capture facets of impulsivity³⁷, did not moderate the relationship between urge and dependence. Thus, the current results suggest that n-back accuracy (a component of d' and hit rate) appears to be an important factor in moderating the relationship between urge and dependence, whereas impulsivity as measured by FA, was not a significant moderator.

Findings may also suggest that the most effective interventions might target negative affect (e.g. cognitive behavioral therapy or behavioral activation), urge (e.g. varenicline or nicotine replacement therapy), and executive function simultaneously in order to prevent multiple pathways to relapse. Whereas many studies have examined the effects of interventions that improve negative emotionality on smoking cessation success^{43,44}, as well as the effects of nicotine replacement therapy or pharmacotherapies on cessation, and even some combining them⁴⁵ – none, to our knowledge, also effectively target executive function deficits simultaneously. Strengthening executive control (i.e. working memory) may provide protection to lapse in the face of inevitable acute changes in affect and urge that may occur despite successful initial improvement via targeted intervention.

The current study has several limitations, most notably, those inherent to a cross-sectional, correlational, design. This approach precludes causal interpretation of the relationship between variables. Second, select variables within each functional domain were assessed, other variables within the same domain may share different relationships among one another in relation to nicotine dependence. Several variables examined relied on self-report and thus

include limitations inherent to this mode of assessment. Lastly, inclusion criteria in the current study included elevated depressive symptoms (CESD-6), although this is not a high level of symptoms, and is indeed an ideal criterion for the focus of this analysis – it may affect the ability for the results presented herein to generalize. Similarly, results of the current study may be limited to smokers motivated to quit (all participants were seeking treatment), and to those with long smoking histories. Future studies examining how negative affect, urge to smoke, and WM affect nicotine dependence in a prospective design are required to support the current results. Despite its limitations, this cross-sectional data provides valuable information toward future studies that could identify causal relationships between these functional domains in addiction. An ideal design would include data collected prospectively on multiple variables within each functional domain in order to allow for the formation of latent variables, and in turn, their effects on dependence or relapse.

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Model 1:

Elevated negative affect was associated with greater urge to smoke, which in turn, was associated with higher levels of nicotine dependence. The indirect effect of Negative Affect on FTND through Craving was significant = .029*, 95% CI [.008 - .059].

* = $p < .05$

** = $p < .01$

Model 2:

The relationship between urge to smoke and nicotine dependence was moderated by WM; for those with WM scores at the sample mean (25.7) and 1SD below the mean, craving was associated with increased dependence, for those high in WM (1SD above mean) the effect of craving on dependence was not significant. Moderated mediation index = -0.069*, 95% CI [-.1663, -0.0076].

* = $p < .05$

** = $p < .01$

Figure 1:
Mediation and Moderated Mediation Models

Table 1:

Descriptive Statistics and Zero-order Correlations of Key Variables

Scale	<i>M</i>	<i>SD</i>	Correlations			
			1	2	3	4
1. Negative Affect (PANAS-NA)	18.83	6.8	1			
2. Urge to Smoke (MNWS)	6.51	1.7	.309**	1		
3. Working Memory (N-back hits)	25.7	3.6	.018	.012	1	
4. Nicotine Dependence (FTCD)	5.28	2.0	.066	.294**	.021	1