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Pharmacological, sensorimotor, and expectancy effects on tobacco withdrawal: a preliminary study

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Objective Research designs for parsing the mechanisms underlying tobacco withdrawal are scant. This study introduced a novel research design that simultaneously manipulated three tobacco withdrawal mechanisms: pharmacological (nicotine dissipation), sensorimotor (elimination of the smoking ritual), and expectancy (activation of beliefs regarding the effects of nicotine deprivation), permitting examination of the effects of each mechanism while holding the other two mechanisms constant.
Methods Following overnight abstinence, 32 regular cigarette smokers were randomized in a 2 (expectancy: told patch contains nicotine versus told placebo patch) × 2 (drug: receive 21-mg transdermal nicotine patch versus receive placebo patch) × 2 (sensorimotor: smoke very low nicotine content cigarettes versus no smoking) full factorial between-subjects design. Participants repeatedly completed measures of craving, affect, and anticipated pleasure from and desire for rewarding experiences, followed by a smoking lapse analog task.
Results Receiving nicotine (versus placebo) increased positive affect and anticipated pleasure from and desire for reward. Expecting nicotine (versus placebo) reduced negative affect and increased smoking delay. Sensorimotor stimulation from smoking (versus no smoking) reduced smoking urge and behavior.
Conclusion Results provided initial validation of this novel three-mechanism design. This design can be used in the future to advance understanding and treatment of tobacco withdrawal. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—abstinence; expectancy; nicotine; sensorimotor; tobacco; withdrawal

INTRODUCTION

The tobacco withdrawal syndrome—a collection of unpleasant symptoms reflecting psychobiological changes that emerge upon the cessation of chronic smoking—is a key feature of tobacco addiction (Leventhal *et al*., 2010; American Psychiatric Association, 2013). Common symptoms of tobacco withdrawal include increased tobacco craving, concentration difficulties, hunger, and negative affect (NA) and decreased heart rate (HR) and blood pressure (BP) (Hughes, 2007; Leventhal *et al*., 2010), and there is also growing evidence that anhedonia (i.e., lack of interest or pleasure) and diminished positive affect (PA) are important aspects of tobacco withdrawal (Dawkins *et al*., 2006; Leventhal *et al*., 2010; Cook *et al*., 2015). Furthermore, one overt behavioral manifestation of tobacco withdrawal is the resumption of smoking (or the inability to resist smoking), which has been studied in the laboratory utilizing analog behavioral choice measures that present individuals with choices to either smoke or forgo the opportunity to smoke to earn money (McKee *et al*., 2006).

Three key biobehavioral changes ensue when people stop smoking that may underpin the expression of withdrawal symptoms: (1) pharmacological—disruptions of biological homeostasis caused by nicotine removal and dissipation of nicotine's acute pharmacological effects; (2) cognitive-expectancy—activation of beliefs about the effects of stopping smoking (e.g., "Without nicotine, I will be so irritable I won't be able to function."); and (3) sensorimotor—elimination of the smoking ritual, including the act of lighting and puffing a cigarette, the sensations of smoke in the airways, and the taste and smell of the cigarette (Shiffman *et al*., 2004; Hughes, 2007). Extant research suggests that pharmacological, sensorimotor, and expectancy processes each play a role in the development of withdrawal symptoms during

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smoking abstinence. To date, however, no study has simultaneously manipulated all three of these mechanisms, which does not permit isolation of the individual effects of each of these mechanisms on the expression of tobacco withdrawal while holding the other two mechanisms constant. For instance, some prior studies have manipulated pharmacological (nicotine versus placebo patch) and sensorimotor factors (very low nicotine content [VLNC] cigarettes versus no cigarettes) but have not concomitantly manipulated expectancies about the dose of nicotine received (Rose *et al*., 2000; Rose *et al*., 2003; Tidey *et al*., 2013). Other studies have utilized a balanced placebo design in which participants are randomly assigned to being told they will receive nicotine or placebo (i.e., dose expectancy manipulation) without simultaneously manipulating sensorimotor stimulation (Juliano and Brandon, 2002; Perkins *et al*., 2004; Perkins *et al*., 2006; Kelemen and Kaighobadi, 2007; Perkins *et al*., 2008; Perkins *et al*., 2009; Juliano *et al*., 2011). In order to advance laboratory research that aims to isolate unique biobehavioral mechanisms underlying the expression of the tobacco withdrawal phenotype, it is important to develop novel methodologies that experimentally parse each of these three putative underpinnings of tobacco withdrawal using a single experimental design.

The purpose of the current laboratory experiment of regular cigarette smokers was to introduce and conduct a preliminary validation of a novel design that simultaneously manipulated three biobehavioral mechanisms of tobacco withdrawal (i.e., pharmacological, sensorimotor, and expectancy), thus allowing us to examine the individual effects of each mechanism while holding the other two mechanisms constant. We applied a comprehensive assessment strategy spanning both well-tested withdrawal outcomes (i.e., cardiovascular activity, NA, PA, smoking urge, and overall withdrawal symptomatology) and more novel outcomes (i.e., two components of hedonic processing: desire to experience reward and anticipated pleasure from reward, and performance on a smoking lapse analog task that measured the ability to resist smoking). In conducting the current experiment, we aimed to: (1) validate a novel paradigm that can be used in future studies that may benefit from isolating the three mechanisms underlying tobacco withdrawal (e.g., genetic association studies of withdrawal endophenotypes, medication development research for smoking cessation, or research on individual difference characteristics that moderate withdrawal) and (2) provide preliminary data on specific manifestations of tobacco withdrawal (e.g., anhedonia versus NA versus smoking urge) that may be linked to distinct underlying mechanisms.

METHODS

Participants were 32 smokers (44% women; *M* age = 50 years) recruited from the Los Angeles area (69% Black people; 31% White people). Participants' mean score on the Fagerström Test for Nicotine Dependence was 5.5 ($SD = 1.9$), indicative of moderate dependence (Fagerstrom *et al*., 1990). Inclusion criteria required participants to be fluent in English, 18 or more years of age, and a regular smoker of 10–30 cigarettes per day during the past 2 or more years. Exclusion criteria included baseline breath carbon monoxide (CO) $<$ 10 ppm, psychiatric medication use, positive urine pregnancy test, prior nicotine patch use or nicotine patch medical contraindication, and non-nicotine substance dependence, mood disorder, or psychotic symptoms (First *et al*., 2002). Study completers were paid US$195. The University of Southern California Institutional Review Board approved the protocol.

Design

This study used a 2 (expectancy: told nicotine patch [$n = 16$] versus told placebo patch [$n = 16$]) $\times$ 2 (drug: receive nicotine patch [$n = 16$] versus receive placebo patch [$n = 16$]) $\times$ 2 (sensorimotor: VLNC [$n = 16$] cigarettes versus no smoking [$n = 16$]) full factorial between-subjects design in which tobacco-deprived participants were randomized to one of eight conditions (four participants each): (1) told nicotine/receive nicotine/smoke VLNC cigarettes; (2) told nicotine/receive placebo/smoke VLNC cigarettes; (3) told placebo/receive nicotine/smoke VLNC cigarettes; (4) told placebo/receive placebo/smoke VLNC cigarettes; (5) told nicotine/receive nicotine/no smoking; (6) told nicotine/receive placebo/no smoking; (7) told placebo/receive nicotine/no smoking; and (8) told placebo/receive placebo/no smoking. For the sensorimotor factor, participants randomized to the VLNC smoking group were accurately told that the cigarettes contained no nicotine in order to disentangle the effect of sensorimotor stimulation from smoking from that of nicotine expectancies. We only examined the main effects for between-subjects factors, given that this is a preliminary study with a small sample size that is underpowered to detect interaction effects.

Procedure

Baseline session. After passing the eligibility screening, participants completed an informed consent and baseline questionnaires and were instructed not to smoke after 9:00 PM on the night prior to the next (experimental) session.

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Experimental session. Figure 1 presents the timeline of experimental session procedures. Participants with CO > 9 or positive for alcohol were allowed to reschedule. During dose instruction, experimenters informed participants that the patch contained no nicotine or a standard dose of nicotine replacement used on the first day of smoking cessation. Experimenters and participants were both blind to drug assignment. Those in the receive-nicotine and receive-placebo groups received a transdermal 21-mg NicoDerm CQ nicotine patch (GlaxoSmithKline, Brentford, UK) and a matching placebo patch (Clinical Trial Services, Salt Lake City, UT, USA), respectively. Patches were placed on the upper back and concealed with a bandage treated with capsaicin 0.075% cream to prevent nicotine detection (Gilbert *et al*., 2005). Participants who smoked VLNC cigarettes (nicotine yield 0.04 mg; tar yield 4 mg) were cued to smoke with a 2.5-s inhalation interval, 3.5-s exhalation interval, and 20-s inter-puff rest period to approximate regular smoking patterns as in prior work (Kelly *et al*., 1990).

Outcome measures. Before patch administration or instructions (9:30) and every 30 min thereafter for 3.5 h, the following measures were completed: (1) BP; (2) HR, (3) Brief Questionnaire of Smoking Urges (Cox *et al*., 2001), (4) Positive and Negative Affect Schedule (Watson *et al*., 1988), (5) Minnesota Nicotine Withdrawal Scale; and (6) Tripartite Pleasure Inventory Responsivity and Desire scales, to assess two dimensions of hedonic processing (Tripartite Pleasure Inventory, Responsivity scale: anticipated pleasure from rewarding experiences, and Tripartite Pleasure Inventory, Desire scale: desire for rewarding experiences; Leventhal *et al*., 2012). Each subjective measure instructed the participants to rate their experiences at the current moment, and composite score outcomes were calculated as average item scores. In between the completion of each assessment (which took approximately 7–10 min), participants were given the option to read magazines we provided or their own reading material from home.

Next, participants completed the smoking lapse analog task (McKee *et al*., 2006), which assessed the ability to resist smoking. The task begins with the delay period: Participants are told they can start smoking their usual brand cigarettes at any time over the next 50 min, but that for each 5 min they delay smoking, they earn US$0.20. When participants indicate they want to smoke (or after 50 min), they begin the self-administration period: Participants are told they can smoke as much as they want over the next 60 min but will deduct US$0.20 from a US$1.60 credit for each cigarette they light. The task terminates at the end of the 60-min self-administration period, which is followed by a no-smoking rest period that lasts 120–170 min depending on the length of delay period. The reason for including the rest period is to prevent minimization of smoking during the task due to expecting an impending opportunity to smoke directly afterwards. Besides being allowed to smoke during the self-administration period, participants are only allowed to sit quietly or walk and look around the room (and thus are not allowed to sleep, eat, read, write, sing, exercise, use technology, etc.) during both task periods and the rest period. Outcome variables were minutes before initiating smoking (range 0–50) and number of cigarettes smoked/purchased (range 0–8). Following the rest period, participants completed an end of study questionnaire, which asked whether they believed they had received a patch with nicotine or no nicotine (to assess the expectancy manipulation).

Data analysis. Alpha (two-tailed) was set at 0.05. A four-factor mixed analysis of variance (ANOVA) with time as an additional within-subjects factor (times 1–8) was used to analyze the manipulation main effects and the manipulation × time interactions for each repeated measure outcome. A three-way between-subjects expectancy × drug × sensorimotor ANOVA was used

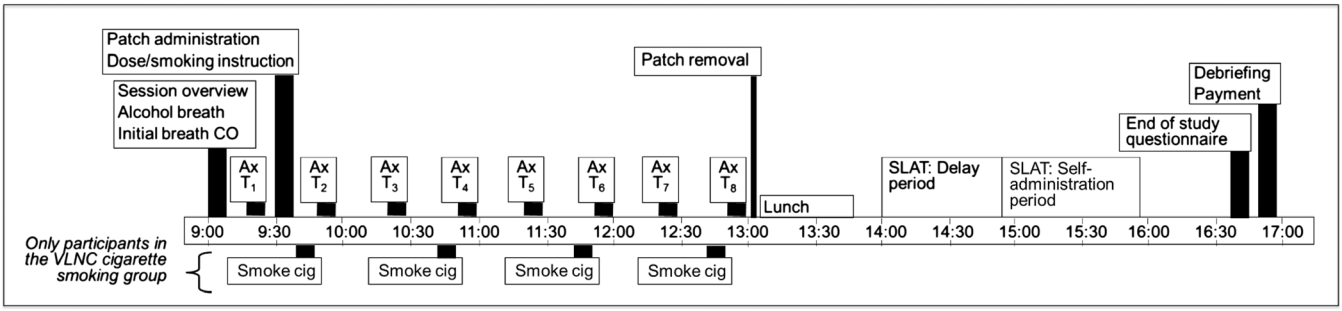

Figure 1. Timeline of experimental procedures. Ax, assessment with subjective measures at times 1–8 (Ax T_1 = pre-manipulation assessment); SLAT, smoking lapse analog task; VLNC, very low nicotine content

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to analyze the main effects of experimental manipulations on smoking lapse analog task outcomes, which were assessed at only a single time point in the study.

RESULTS

Preliminary analyses

Fisher's exact tests and one-way ANOVAs revealed that groups did not differ significantly in respect to sex, race, age, or Fagerström Test for Nicotine Dependence score.

Primary analyses

The main and interaction effects of experimental manipulations on repeated measures are shown in Table 1. Subjective assessments over time for significant interaction effects are shown in Figure 2, and performance on the smoking lapse analog task is shown in Figure 3. Only significant effects are detailed in the succeeding texts.

Drug effects. A main effect of drug on PA was found, such that the level of PA averaged across the repeated assessments was higher in the receive-nicotine (versus receive-placebo) group. Drug × time interactions on PA, Tripartite Pleasure Inventory, Responsivity scale, Tripartite Pleasure Inventory, Desire scale, and smoking urge were also found, such that PA, anticipated pleasure from reward, desire to experience reward, and urge decreased at a faster rate in the receive-placebo (versus receive-nicotine) group (Figure 2a, b, c, and d). Drug × time interactions were also found for systolic BP and HR, such that systolic BP increased at a faster rate and HR decreased at a slower rate (remained stable) in the receive-nicotine (versus receive-placebo) group (Figure 2e and f).

Expectancy effects. An expectancy × time interaction on NA was found, such that NA decreased over time at a faster rate in the told-nicotine (versus told-placebo) group (Figure 2g). On the lapse analog task, those randomized to the told-nicotine group also delayed smoking usual brand cigarettes longer than those in the told-placebo group ($F_{(1, 28)} = 4.88$, $d = 0.72$; Figure 3a).

Sensorimotor effects. Sensorimotor main effects on NA, overall withdrawal symptoms, and smoking urge were found, such that NA, withdrawal symptoms, and urge were lower when averaged across all assessments in the VLNC (versus no smoking) group. A sensorimotor × time interaction on urge was also found, such that urge decreased to a greater extent over time in the VLNC (versus no smoking) group (Figure 2h). As shown in Figure 3, those randomized to the VLNC (versus no smoking) group delayed usual-brand smoking longer and smoked fewer usual brand cigarettes, respectively ($F_{(1, 28)} = 4.57$, $d = 0.70$; $F_{(1, 28)} = 7.71$, $d = 1.0$).

Supplemental analyses. Four of the 32 (12.5%) participants reported receiving a drug different from the drug they were told they received (i.e., believed they were deceived). Of those, two actually were deceived, and two were not, which is equivalent to a 50/50 chance of correctly guessing. Rerunning analyses with those four participants removed did not alter the statistical significance of findings.

DISCUSSION

Each manipulation significantly altered the expression of tobacco withdrawal in at least some way (effect sizes medium to large in magnitude), providing initial

Table 1. Manipulation main effects and manipulation × time interaction effects on repeated measures

	Expectancy			Expectancy × time			Drug			Drug × time			Sensorimotor			Sensorimotor × time		
Measure	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
PANAS-NA	0.2	0.68	0.01	2.4	**0.02**	0.08	1.4	0.25	0.05	0.6	0.780	0.02	8.4	**0.007**	0.23	0.5	0.83	0.02
PANAS-PA	1.1	0.31	0.04	0.5	0.85	0.02	5.8	**0.02**	0.17	3.4	**0.002**	0.11	1.8	0.190	0.06	1.6	0.15	0.05
QSU-Brief	0.0	0.84	0.00	0.6	0.72	0.02	0.5	0.49	0.02	2.7	**0.012**	0.09	5.3	**0.030**	0.16	5.9	**<0.001**	0.17
MNWS	0.1	0.81	0.00	0.4	0.88	0.02	0.1	0.78	0.00	1.9	0.068	0.06	5.5	**0.026**	0.16	1.2	0.32	0.04
TPI-R	0.0	0.94	0.00	0.3	0.94	0.01	1.9	0.18	0.06	2.1	**0.043**	0.07	0.4	0.510	0.02	0.5	0.80	0.02
TPI-D	0.0	0.92	0.00	0.6	0.72	0.02	1.7	0.21	0.06	3.1	**0.004**	0.10	0.7	0.430	0.02	0.3	0.94	0.01
Systolic BP	2.0	0.17	0.07	1.1	0.38	0.04	0.1	0.74	0.00	3.4	**0.002**	0.11	0.7	0.420	0.02	0.8	0.57	0.03
Diastolic BP	0.9	0.35	0.03	0.6	0.74	0.02	0.2	0.66	0.01	0.7	0.640	0.03	3.1	0.088	0.10	0.8	0.55	0.03
HR	0.0	0.88	0.00	0.6	0.76	0.02	2.5	0.12	0.08	2.9	**0.007**	0.09	0.4	0.520	0.02	1.1	0.37	0.04

PANAS-NA, Positive and Negative Affect Schedule, Negative Affect scale; PANAS-PA, Positive and Negative Affect Schedule, Positive Affect scale; QSU-Brief, Brief Questionnaire of Smoking Urges; MNWS, Minnesota Nicotine Withdrawal Scale; TPI-R, Tripartite Pleasure Inventory, Responsivity scale; TPI-D, Tripartite Pleasure Inventory, Desire scale; BP, blood pressure; HR, heart rate.
Degrees of freedom for main and interaction effects are (1,28) and (7,196), respectively.
Significant *p*-values are displayed in bold print.

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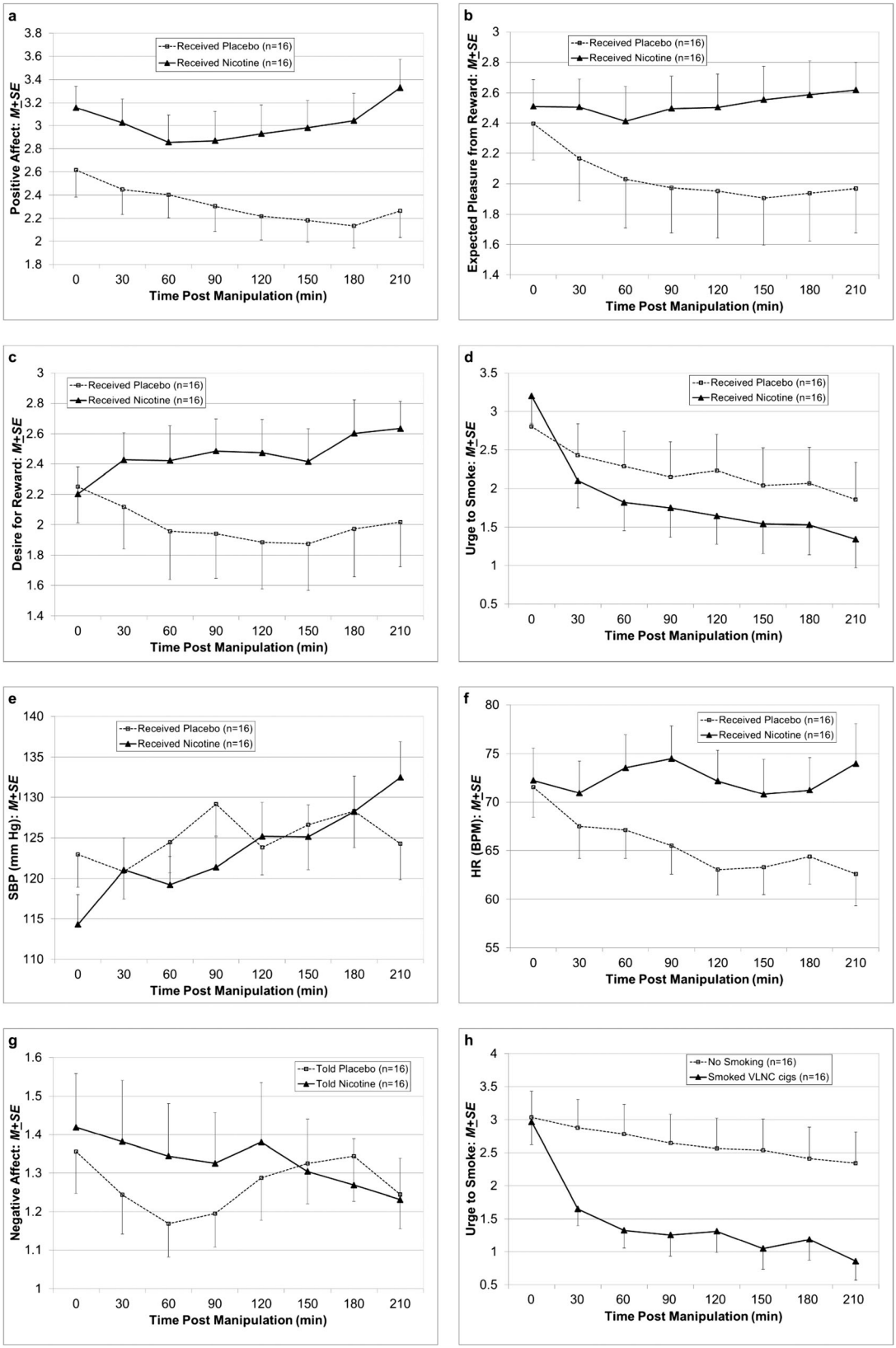

Figure 2. Subjective assessments over time (times 1–8) for significant interaction effects in the expectancy, drug, and sensorimotor manipulation groups. VLNC, very low nicotine content; HR (BPM), heart rate in beats per minute; SBP (mmHg), systolic blood pressure in millimeters of mercury

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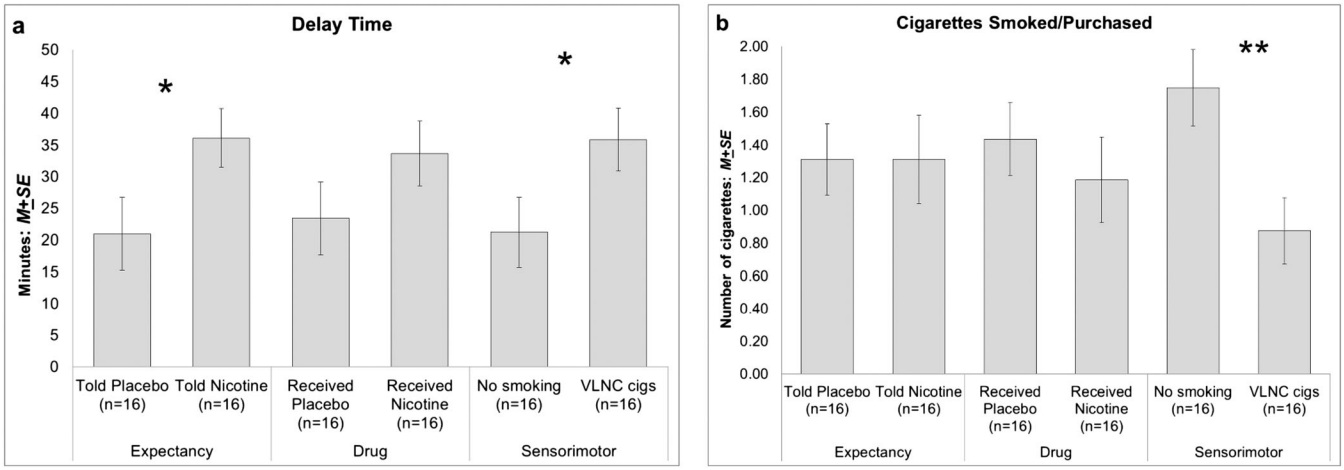

Figure 3. Performance on the smoking lapse analog task in the expectancy, drug, and sensorimotor manipulation groups. Delay time is the amount of time participants chose to delay smoking (range 0–50 min) after being allowed to smoke. Cigarettes smoked/purchased is the number of cigarettes (range 0–8) that participants paid to smoke during the hour after the delay period. VLNC, very low nicotine content. $*p < .05$, $**p = .01$

validation of this novel three-mechanism design. Furthermore, the pattern of effects of each mechanism across disparate manifestations of tobacco withdrawal occurred in a non-uniform fashion.

The expectation of having received nicotine (versus the expectation of having received placebo) facilitated reductions in NA and reduced motivation to initiate smoking of preferred brand cigarettes on the smoking lapse analog task (4.5–6.5 h after the expectancy manipulation). These findings partially concord with prior work (Juliano and Brandon, 2002; Juliano *et al*., 2011; cf. Perkins *et al*., 2006; Perkins *et al*., 2008) and extend past results both by utilizing a novel outcome measure (i.e., willingness to delay smoking for money) and by experimentally manipulating both drug and sensorimotor stimulation to hold these factors constant. Hence, these findings suggest a unique influence of expectancy on NA and motivation to resume smoking during abstinence.

Nicotine delivery buffered against the declines in PA and two components of hedonic processing: anticipated pleasure from and desire for reward. Reward anticipation is an important aspect of reward functioning that may affect the likelihood of seeking out nondrug reinforcers following a cessation attempt (Der-Avakian and Markou, 2012). Although previous studies have shown that nicotine replacement therapy (e.g., nicotine lozenge and/or transdermal nicotine patch) increases PA and pleasure expectations and experiences in smokers during tobacco abstinence relative to placebo (Dawkins *et al*., 2006; Gilbert *et al*., 2008a, 2008b; Donny and Jones, 2009; Cook *et al*., 2015), this is the first study to show such an effect on desire for rewarding experiences. Notably, these findings are consistent with prior experimental literature (mostly from laboratory animals) indicating that nicotine has reinforcement enhancing effects on nondrug appetitive stimuli (Caggiula *et al*., 2009; Perkins and Karelitz, 2014). Taken together, research suggests that tobacco withdrawal leads to a narrowing of environmental rewards due to decrements in both reward anticipation and response (as well as in desire for reward), which is an effect that is reversed by nicotine administration. Thus, upon quitting, dependent smokers might resume smoking to alleviate anhedonia induced by tobacco withdrawal, which may be specifically related to nicotine deprivation. In the current study, nicotine also increased systolic BP and prevented the HR-lowering effects of tobacco withdrawal. These findings are consistent with prior research on the cardiovascular effects of tobacco abstinence and nicotine replacement therapy (Najem *et al*., 2006; Hughes, 2007; Gehricke *et al*., 2009; Leventhal *et al*., 2010) but extend past results by being the first to document such effects when holding sensorimotor and expectancy effects constant via simultaneous manipulation.

The lack of a significant nicotine effect on NA is unexpected given that a number of prior placebo-controlled studies have reported that the nicotine patch alleviates withdrawal-related NA (Ferguson and Shiffman, 2014). It is possible that the current study lacked statistical power to detect effects because of small sample size, although given the small effect size of the drug × time interaction on NA in this study ($\eta_p^2 = 0.02$), if a reliable effect was not detected, it was likely modest. Another possibility is that any effect of nicotine *per se* on NA is likely to be modest. Indeed, a recent tightly

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controlled lab experiment that was adequately powered ($N = 104$) showed that nicotine did not uniquely reduce NA during abstinence when parsed from other factors confounded with smoking, such as sensorimotor stimulation (Perkins *et al.*, 2010). Furthermore, in many placebo-controlled nicotine replacement studies, expectancy is often conflated with drug condition because the study blind is commonly not upheld, as participants tend to accurately guess their drug assignment beyond chance when expectancy is not directly manipulated (Mooney *et al.*, 2004). Thus, the drug effect on NA in placebo-controlled nicotine replacement studies might be inflated by concomitant expectancy effects. It is possible that when the effect of nicotine is parsed from expectancy and sensorimotor influences as was done in the current design, the remaining pharmacological influence of nicotine *per se* on NA is quite modest. Future work in larger samples will be required to more thoroughly evaluate this hypothesis.

Sensorimotor stimulation from smoking VLNC cigarettes (versus no smoking) reduced the urge to smoke over time and suppressed the motivation to initiate and continue smoking preferred brand cigarettes on the smoking lapse analog task. These findings are consistent with past research indicating that smoking denicotinized cigarettes acutely suppresses craving and smoking behavior (Rose *et al.*, 2000; Rose *et al.*, 2003; Przulj *et al.*, 2012; Tidey *et al.*, 2013) and extend prior results by essentially duplicating them when holding the expectancy and drug effects constant through experimental manipulation. Sensorimotor stimulation from smoking also had a main effect on overall withdrawal symptoms. We interpret this finding with caution given the absence of a sensorimotor × time interaction effect on withdrawal symptoms and the evidence of modest nonsignificant differences in withdrawal symptoms at the premanipulation time 1 assessment ($p = 0.14$; $d = 0.54$), which could have spuriously influenced this finding.

This study has several limitations. Because the sample was small, it was underpowered to detect small effects and did not allow for the analysis of potential interactions between experimentally manipulated factors. Furthermore, because this was a preliminary study and we did not want to overlook any potential effects of the manipulations across various expressions of withdrawal that could be followed up in future work, we did not correct the significance level for multiple testing. Hence, some of the significant findings with less extreme *p*-values should be interpreted with caution, and some instances in which significant effects were not found may reflect type-II errors. In addition, because we examined non-quitting smokers during a brief duration of abstinence, current findings may not generalize to longer periods of abstinence or to smokers who are attempting to quit smoking. Thus, this study is best suited for supporting the validity of the experimental design and provides only preliminary results regarding the nature of linkages between particular biobehavioral mechanisms and specific manifestations of tobacco withdrawal, which should be definitively addressed in future work utilizing larger samples and extending to treatment-seeking smokers and different durations of abstinence.

CONCLUSION

The novel paradigm validated in this study may benefit future investigations of tobacco withdrawal. This laboratory model could be used to examine if genetic and other individual difference factors that modulate expression of the tobacco withdrawal phenotype exert their influence on withdrawal by interacting with a single mechanism and having less robust effects via the other two mechanisms (e.g., cholinergic nicotinic receptor gene variation and pharmacological mechanisms). Hence, for instance, this design could be leveraged to isolate purer pharmacologically mediated endophenotypes of withdrawal in molecular genetic studies aiming to parse out error in phenotype modeling. This research may also support efforts to match treatment type to a smoker's withdrawal profile. For example, if deficient PA and anhedonia are reliably linked to nicotine-mediated pharmacological mechanisms in future work, patients wanting to quit smoking who tend to experience such symptoms may benefit from pharmacological agents that modulate the nicotinic receptor system (e.g., nicotine replacement and varenicline) as front line treatments rather than solely utilizing cognitive or behavioral interventions. In sum, experimental models such as the approach used here may be of great scientific and clinical value to tobacco addiction research.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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