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Effects of galantamine on smoking behavior and cognitive performance in treatment-seeking smokers prior to a quit attempt

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Abstract

Objective: Drugs that enhance cholinergic transmission have demonstrated promise treating addictive disorders. Galantamine, an acetylcholinesterase inhibitor, may reduce cigarette smoking in otherwise healthy treatment-seeking smokers.

Methods: The current study is a double-blind, placebo-controlled, study that randomized daily smokers ($n = 60$) to receive one of two doses of galantamine extended release (8 or 16 mg/day), or a placebo treatment. Participants completed a smoking choice task as well as study measures and cognitive tasks in the laboratory and daily life using ecological momentary assessment. Analysis focused on smoking behavior and satisfaction, cognitive performance, and decision to smoke prior to a quit attempt.

Results: Linear mixed models demonstrated that, compared with placebo, both doses of galantamine reduced smoking in a laboratory choice task ($p = 0.006$) and decreased urine cotinine levels, but not self-reported cigarettes, during the pre-quit period ($p = 0.007$). Treatment had minimal effect on smoking satisfaction or cognitive performance.

Conclusions: The results suggest that galantamine reduces nicotine intake but it is unlikely that galantamine improves cognitive performance in otherwise healthy, treatment-seeking smokers. Larger randomized clinical trials can determine if galantamine adjunctive to addiction treatment can improve smoking treatment outcomes.

Keywords

cognitive performance; ecological momentary assessment; galantamine; smoking; tobacco

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

1 | INTRODUCTION

Drugs that enhance cholinergic transmission have recently been evaluated for pharmacological treatment of addictive disorders, including tobacco use disorder (TUD; Sofuoglu, DeVito, Waters, & Carroll, 2013). Galantamine, a Food and Drug Administration approved medication for treatment of cognitive deficits associated with Alzheimer's disease (Birks, 2006), increases synaptic acetylcholine levels by inhibiting acetylcholinesterase, an enzyme that breaks down acetylcholine. Galantamine also directly stimulates $\alpha 7$ and $\alpha 4\beta 2$ nicotinic acetylcholine receptors (nAChRs) via its positive allosteric modulator actions (Samochocki et al., 2003). Because nAChRs represent an important treatment target for TUD (Le Foll et al., 2016), further examination of galantamine's efficacy as a treatment for TUD is warranted.

Galantamine administration reduces nicotine self-administration and prevents reinstatement of nicotine-seeking behavior in rodents (Hopkins, Rupprecht, Hayes, Blendy, & Schmidt, 2012; Liu, 2013), but results from human studies have been mixed (Diehl et al., 2006; Kelly et al., 2008). A recent study evaluated the effects of 2 weeks of galantamine on smoking behavior in otherwise healthy, treatment-seeking smokers (>10 cigarettes per day [cpd]). Relative to placebo, smokers treated with galantamine reported a significant reduction in cpd, and, compared with baseline, the galantamine group reported less satisfaction and reward from smoking (Ashare et al., 2016). Taken together, galantamine may be an effective pharmacological aid for the treatment of TUD, but its effects on smoking behavior and broader outcomes (e.g., cognitive function) in laboratory and natural settings remain unexamined.

We conducted a double-blind, placebo-controlled study that randomized daily smokers to receive galantamine extended release (8 or 16 mg/day), or placebo for 7 weeks. Our goals were to evaluate recent findings (i.e., Ashare et al., 2016) in an inclusive population of healthy smokers using laboratory and field-based assessments (ecological momentary assessment [EMA]). To evaluate the effects of galantamine in the absence of other interventions during ad-lib smoking, we evaluated behavior prior to a quit attempt (e.g., Weeks 1–4). Participation in the post-quit portion of the study was optional (see Supporting Information). We hypothesized that, compared with placebo, galantamine would reduce smoking behavior and decisions to smoke in a smoking choice task. Regarding its mechanism of action, we predicted that galantamine would attenuate subjective satisfaction/pleasure from smoking and improve performance on cognitive tasks measured in the laboratory and the field.

2 | METHOD

2.1 Participants

A total of 60 participants were enrolled and randomized (Figure 1). The overall sample was 62% male, predominantly Caucasian (77%), with a mean age of 38.3 years ($SD = 10.0$), and reported smoking an average of 13.7 ($SD = 6.9$) cpd. Treatment groups did not differ by any characteristics measured (p 's > 0.12), except cpd ($p = 0.03$). Post hoc comparisons revealed a significant difference between the 8- and 16-mg groups ($p = 0.02$); all comparisons with

placebo were not significant (p 's > 0.28). The Human Subjects Subcommittee at the VA Connecticut Healthcare System and Institutional Review Board at Yale University approved all study procedures.

2.2 Treatment and study protocol

After a baseline visit, the study contained two phases: Phase 1 (pre-quit; Weeks 1–4) and Phase 2 (post-quit; Weeks 5–7). Outline of study protocol can be found in Figure 2. The current manuscript evaluates the effect of galantamine on ad-lib smoking behavior prior to a quit attempt (i.e., Phase 1). For laboratory-based assessments, participants attended twice-weekly visits to complete measures on self-reported nicotine effects, normal smoking behavior, and smoking choice task after 12 hr of abstinence (Tidey, O'Neill, & Higgins, 2000) during Week 3. Participants also completed an EMA paradigm on Week 4. For EMA paradigm, participants were given a personal digital assistant that signaled four assessments at random times each day (random assessments) and permitted user-initiated assessments. Laboratory visits included assessments for smoking satisfaction and pleasure from cigarettes over the past week (1 = *not at all*, 7 = *extremely*), breath CO (Vitalograph, Lenexa, KS), urine cotinine, and 7-day substance use calendar. Urine cotinine was positively correlated with mean self-report cigarettes smoked in the same week ($r = 0.34$, $p < 0.001$). EMA surveys included real-time reports of smoking behavior and items assessing smoking satisfaction (1 = *not at all*, 7 = *extremely*) and pleasure (1 = *not at all*, 7 = *extremely*) for the last cigarette smoked.

All participants completed the Go/No-go task (Sofuoglu, Waters, Mooney, & Kosten, 2008) and a Rapid Visual Information Processing (RVIP) task (Foulds et al., 1996) at baseline and throughout study during laboratory-based visits and EMA. For the laboratory-based and EMA Go/No-go tasks, 225 numbers (range = 1–9) were presented for 250 ms followed by a 900-ms mask (i.e., one letter every 1,150 ms). Participants were instructed to press the response button for every number except “3.” The primary measures on the Go/No-go task were number of commission errors on the no response target (i.e., responding to the number “3”). Other performance measures included number of omission errors (i.e., not responding to numbers other than “3”) and average response reaction time. Reaction times less than 100 ms were discarded from analysis. For the laboratory RVIP task, a series of single digits were presented at a rate of 100 digits per minute. Participants were instructed to detect a three target sequences (“2-4-6,” “3-5-7,” and “4-6-8”) and press the space bar within 1,800 ms of the last target being displayed. To reduce the impact of practice effects after repeated administration during EMA, targets were defined as three consecutive odd digits (e.g., 7-9-3) or three consecutive even digits (e.g., 2-8-6). Participants were instructed to press the response button as quickly as possible after detecting a target. For both the laboratory and EMA tasks, a total of 32 targets were presented (eight targets per minute) with 5 to 30 digits between each target. Performance measures on the RVIP were the percentage of targets correctly detected (i.e., hits), average response latency, and number of false positives. During EMA, the personal digital assistant was programmed to administer either the Go/No-go task or the RVIP task (in an alternating sequence) using the same parameters as laboratory versions.

2.3 Data reduction and analytic plan

For RVIP performance, data from Phase 1 EMA (i.e., Week 4) were excluded for the following reasons. Data from one assessment (0.31% of 327 total assessments) were excluded due to experimenter error in set up of sequences (excessive number of trials). Data from 108 assessments (33.18% of 326 assessments) were excluded due to no responses (either hits or false alarms) during the task, indicating that the participant was likely not attempting to complete the task appropriately. Of the remaining 218 assessments, data from 22 assessments (10.09% of 218 assessments) were excluded due to an excessive number (>100) of false alarms, indicating that participants were pressing the response button repeatedly. After these exclusions, 37 of the 39 participants (94.87%) provided RVIP data 16 mg GAL ($n = 14$); 8 mg GAL ($n = 14$); placebo ($n = 9$).

For Go/No-go performance, data from Phase 1 EMA were excluded for the following reasons. Data from 16 assessments (5.02% of the total 319 Go/No-go assessments) were excluded due to experimenter error in set up of sequences (e.g., excessive number of trials or incorrect sequences). Data from 71 assessments (23.43% of 303) were excluded due to an excessive number (>100 out of 200) of errors on Go trials (failing to press a button for a non-3), indicating that participants were not performing the task appropriately. After these exclusions, 32 of the 39 participants (82.05%) provided Go/No-go data 16 mg GAL ($n = 11$); 8 mg GAL ($n = 14$); placebo ($n = 7$).

Linear mixed models (LMM; SAS Systems, Cary, NC) tested the effect of Treatment on outcomes including measures of cognitive performance (RVIP and Go/No-go), smoking behavior (self-administration in smoking choice task, self-reported cpd, and urine cotinine), and subjective effects from smoking (i.e., satisfaction and pleasure). For all analyses, Treatment (3-level multinomial variable: 16 mg vs. 8 mg vs. placebo) was entered as level 2 variable, and Visit Number (treated as random) was included as a level 1 covariate. The baseline value of each dependent variable was included as a level 2 covariate. Continuous outcome models included a random (subject-specific) intercept and an autoregressive model of order 1 for the residuals within participants. Analyses tested the main effects of Treatment and Time (Visit Number), and the Treatment $\times$ Time interaction. For EMA data, Assessment type (random assessments vs. participant-initiated) was included as a level 1 covariate, and analyses focused on the main effect of Treatment.

Compliance with medication via pill count was excellent at 96.8%. Summary statistics for all smoking behavior are in Table 1 and cognitive performance in Table 2. All models were rerun with cpd entered as a covariate, and results were unchanged (Table S1).

3 RESULTS

3.1 Smoking behavior

LMMs conducted on laboratory data revealed a significant effect of Treatment on urine cotinine, reflecting a reduction in urine cotinine in both galantamine groups compared with placebo (Table 3). There was a significant main effect of Time on cpd and satisfaction/pleasure, such that, over time, all participants reported fewer cigarettes smoked as well as

less pleasure and satisfaction from smoking. There were no significant Treatment $\times$ Time interactions.

On the smoking choice task, there was a significant main effect of Treatment, $F(2, 47) = 5.73$, $p = 0.006$. Planned comparisons revealed that individuals in the placebo group chose to smoke more frequently than those in the 8 mg ($p = 0.02$) and 16 mg ($p = 0.007$) galantamine groups; the comparison between the 8 and 16 mg groups was not significant ($p = 0.97$).

LMMs on EMA field data revealed no significant effects of Treatment.

3.2 Cognitive performance

LMMs of laboratory data revealed an effect of Time such that participants improved performance on the RVIP task irrespective of Treatment. Analysis of EMA data revealed that galantamine administration was associated with decreased latency to respond on the RVIP task. All other main effects and Treatment $\times$ Time interactions were nonsignificant (Table 3).

4 DISCUSSION

In this pilot study, galantamine, compared with placebo, reduced self-administration in a smoking choice task and reduced urine cotinine levels during the pre-quit period. Notably, galantamine did not affect self-reported cpd, smoking satisfaction/pleasure, or cognitive performance in the laboratory or the field. These findings partially support those of Ashare et al. that reported galantamine reduced smoking behavior (i.e., cotinine); in contrast, we did not detect decreased cpd or satisfaction/pleasure from smoking associated with galantamine administration in either laboratory or EMA data. It is possible that the inclusion of lighter smokers (i.e., >5 cpd) may reduce power to detect smaller decreases in cpd. However, the observed decrease in cotinine in both galantamine groups is strengthened by prior research suggesting that biochemical confirmation of smoking confirmed using cotinine is more reliable than self-report (Connor Gorber, Schofield-Hurwitz, Hardt, Levasseur, & Tremblay, 2009). To better compare laboratory and EMA data, we used a single-item measure of smoking satisfaction and pleasure. For comparison, Ashare et al. used an 11-item scale to quantify the subjective effects of smoking. Accordingly, more comprehensive assessment of smoking satisfaction and pleasure may be necessary to detect an effect of galantamine on smoking satisfaction and pleasure.

Although the exact neural mechanism is unknown, galantamine is believed to reduce smoking behavior via positive allostatic modulation of $\alpha 4\beta 2$ nAChRs in the brain. Preclinical studies have established the role of $\alpha 4\beta 2$ nAChRs in nicotine reinforcement (Maskos et al., 2005; Tapper et al., 2004), and drugs that target $\alpha 4\beta 2$ nAChRs, such as varenicline, are associated with decreased nicotine intake in rodents (George, Lloyd, Carroll, Damaj, & Koob, 2011) and increased smoking cessation in humans (Gonzales et al., 2006). Like varenicline, galantamine is assumed to reduce the subjective effects of acute nicotine exposure thereby decreasing satisfaction and reward from smoking; however, this study did not find any significant effects of galantamine on subjective effects from smoking. Galantamine's capacity to attenuate the reinforcing effects of nicotine may be more evident after acute nicotine exposure, as observed in preclinical and clinical laboratory studies

(Hopkins, Rupprecht, Hayes, Blendy, & Schmidt, 2012; Sofuoglu, Herman, Li, & Waters, 2012). Additionally, cognitive performance was not significantly affected by galantamine administration in the laboratory or during EMA.

By repeatedly assessing cognitive performance in both the laboratory and daily life, we intended to evaluate enhanced cognitive performance as a possible mechanism for reduced smoking or agonist-like effects of galantamine. Indeed, galantamine has been associated with increased cognitive performance in individuals with baseline cognitive deficits such as Alzheimer's disease (Takeda et al., 2006), schizophrenia (Buchanan et al., 2008; Schubert, Young, & Hicks, 2006), and cocaine use disorder (Sofuoglu, Waters, Poling, & Carroll, 2011); but studies failing to replicate cognitive improvements should be noted (Buchanan et al., 2017; Raina et al., 2008). The efficacy for cognitive enhancement as a treatment for drug addictions is still developing (Sofuoglu, DeVito, Waters, & Carroll, 2013). Preclinical studies have also suggested that other positive allosteric modulators of $\alpha 4\beta 2$ nAChRs that do not inhibit acetylcholinesterase reduce nicotine self-administration (Hamouda, Jackson, Bagdas, & Damaj, 2017; Maurer, Sandager-Nielsen, & Schmidt, 2017) and improve cognitive performance (Pandya & Yakel, 2013). The efficacy of these compounds in reducing smoking behavior and enhancing cognition in treatment-seeking smokers may be greater than galantamine and is an important direction for future studies.

5 CONCLUSION

Study limitations include the small sample size, meaning that the study only had good power to detect large effect sizes, and the inclusion of multiple laboratory-based and EMA assessments, which may have increased participant awareness of smoking behavior. Nevertheless, these findings contribute to literature indicating that galantamine reduces smoking behavior prior to a quit attempt. Both 8 and 16 mg/day of galantamine were well tolerated and were not associated with treatment drop out. The observed reduction in cotinine is not likely due to changes in cognitive performance or general decreases in smoking satisfaction/pleasure in healthy smokers. The effectiveness of galantamine may be enhanced in heavier smokers with other concurrent mental health problems such as alcohol use (Diehl et al., 2006; Mann et al., 2006). Galantamine may help improve the efficacy of smoking cessation in these complex clinical populations. Larger randomized clinical trials can determine if galantamine, as well as other positive allosteric modulators of $\alpha 4\beta 2$ nAChRs, adjunctive to addiction treatment can improve smoking treatment outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

CONSORT flow diagram. Missing data: a = technical error, b = participant error, c did not complete ecological momentary surveys. Numbers reflect number of cases (e.g., b2 = data from two participants were lost due to participant error). cpd: cigarettes per day; RVIP: Rapid Visual Information Processing

Phase		Baseline	Phase 1 (pre-quit)				Optional Phase 2 (post-quit)			
			EMA				EMA			
Week		0	1	2	3	4	5	6	7	8
Dose (Randomized @ Week 0)	Placebo	-	0	0	0	0	0	0	0	0
	8mg	-	8	8	8	8	8	8	8	8
	16mg	-	8	8	16	16	16	16	16	16

FIGURE 2.

Study protocol and dosing procedures. Smoking choice task occurred during Week 3. Phase 2 was optional and included a quit attempt during Week 5. EMA: ecological momentary assessment

TABLE 1
Summary statistics on lab and field smoking behavior variables by Training Group and Time

Setting →	Lab	Lab	Lab	Lab	Lab	Lab	Lab	Lab	Field	Lab
Group (mg) ↓	Week →	0	1	1	2	2	3	3	4	4
Lab visit →	0	1	1	2	3	4	5	6	7	8
16	Satisfaction (1–7) ^a	5.52 (1.21)	4.59 (1.79)	4.52 (1.83)	4.20 (1.99)	4.25 (2.10)	4.05 (1.99)	4.45 (2.09)	4.17 (1.92)	4.09 (0.89) 4.25 (1.95)
	Pleasure (1–7) ^a	5.24 (1.37)	4.32 (2.12)	4.43 (1.86)	4.05 (2.09)	4.10 (2.00)	3.85 (2.08)	4.35 (2.13)	4.17 (1.92)	4.13 (0.83) 3.94 (2.11)
	Smoking choice ^b							0.85 (1.35)		
	No. cigs (diary)		7.13 (2.93)		5.64 (3.50)		5.18 (2.65)		5.03 (2.76)	
	Recency past cig (hr)—Field only ^c									2.01 (0.68)
	CO (PPM)	7.82 (7.22)	7.65 (7.54)	6.76 (4.59)	5.70 (5.51)	7.30 (6.80)	6.70 (5.73)	4.80 (3.16)	5.82 (3.96)	6.47 (4.90)
	Cotinine (1–6)	5.27 (1.24)	5.76 (0.70)		5.30 (1.22)		5.25 (1.25)		5.41 (1.00)	
8	Satisfaction (1–7) ^a	5.80 (1.20)	5.21 (1.23)	4.74 (1.52)	4.32 (1.60)	4.28 (1.67)	4.13 (1.75)	4.29 (1.69)	4.06 (1.73)	3.92 (1.17) 4.06 (1.91)
	Pleasure (1–7) ^a	5.50 (1.47)	5.11 (1.37)	4.47 (1.50)	4.42 (1.68)	4.11 (1.60)	4.25 (1.77)	4.29 (1.69)	3.88 (1.82)	3.90 (1.13) 4.00 (1.93)
	Smoking choice ^b							1.00 (1.00)		
	No. cigs (diary)		10.75 (7.28)		9.59 (7.13)		9.03 (7.21)		8.27 (7.01)	
	Recency past cig (hr)—Field only ^c									2.35 (0.70)
	CO (PPM)	9.00 (6.46)	10.74 (6.04)	9.53 (4.73)	8.68 (6.22)	9.44 (6.35)	8.81 (6.67)	7.59 (3.87)	8.80 (5.25)	10.19 (5.87)
	Cotinine (1–6)	5.48 (1.47)	5.53 (0.9)		5.37 (1.42)		5.65 (1.06)		5.31 (1.40)	
0	Satisfaction (1–7) ^a	6.06 (1.00)	5.59 (1.37)	4.76 (1.52)	4.33 (1.05)	4.00 (1.56)	3.87 (1.68)	4.07 (1.27)	3.82 (1.60)	3.67 (1.02) 3.90 (1.52)
	Pleasure (1–7) ^a	5.44 (1.55)	5.18 (1.63)	4.82 (1.78)	4.40 (1.45)	4.27 (1.49)	3.80 (1.90)	4.00 (1.52)	3.82 (1.54)	3.66 (1.01) 3.70 (1.49)
	Smoking choice ^b							3.00 (3.08)		
	No. cigs (diary)		7.83 (3.53)		8.50 (4.88)		7.80 (5.08)		5.88 (5.55)	
	Recency past cig (hr)—Field only ^c									2.11 (0.58)
	CO (PPM)	6.06 (3.58)	8.00 (4.15)	7.71 (4.52)	7.80 (7.26)	7.33 (7.42)	6.80 (5.94)	5.93 (2.56)	9.27 (10.74)	7.55 (8.94)
	Cotinine (1–6)	5.00 (1.32)	5.76 (0.56)		5.93 (0.26)		5.53 (0.74)		5.64 (0.67)	

Note. Data are $M(SD)$. For ecological momentary assessment (EMA) data, n 's for self-report data are 16 mg ($n = 15$); 8 mg ($n = 15$); and placebo ($n = 9$). During Week 4, participants completed 675 assessments (45.78% random assessments, 54.22% participant-initiated assessments).

^a Anchors for smoking satisfaction and pleasure scale for lab and field data were 1 = *not at all* and 7 = *extremely*.

^b Outcome measure for smoking choice task was the number of times an individual chose to smoke (vs. abstain to earn money).

^c Options for smoking recency were 1 = *No cigarettes in past 2 hr*, 2 = *Smoked cigarette within 2 hr*, 3 = *Smoked cigarette within 30 min*, and 4 = *Just smoked/Smoking now*.

TABLE 2

Summary statistics on lab and field cognitive performance variables by Training Group and Time

Group (mg/d)	Setting →		Lab		Lab		Lab		Lab		Field	
	Lab visit →		0	1	1	2	3	5	7			
EMA data												
Week →		0	1	1	2	3	4	Pre-quit				
16	RVIP hits		13.14 (4.92)	15.05 (4.75)	16.45 (5.32)	16.30 (5.99)	16.76 (4.41)	10.50 (7.11)				
	RVIP latency (ms)		453.91 (133.66)	462.48 (168.68)	462.00 (165.96)	438.39 (109.02)	416.49 (104.93)	672.61 (85.36)				
	RVIP false		6.50 (9.09)	6.18 (7.75)	7.00 (11.69)	4.35 (5.23)	4.82 (7.63)	29.02 (26.67)				
	Go/No go commission		11.14 (5.03)	9.59 (7.56)	8.79 (8.30)	9.47 (6.83)	8.06 (7.46)	11.87 (5.20)				
8	Go/No go omission		23.86 (42.7)	28.77 (56.43)	39.89 (71.73)	32.05 (61.08)	46.47 (73.89)	32.86 (25.69)				
	Go/No go RT (ms)		384.89 (70.94)	422.95 (149.19)	444.18 (86.67)	410.69 (71.65)	445.51 (71.41)	360.74 (92.08)				
	RVIP hits		13.84 (6.34)	15.58 (5.06)	16.05 (5.19)	16.69 (6.32)	16.44 (6.14)	8.20 (6.47)				
	RVIP latency (ms)		506.71 (205.34)	502.35 (186.36)	470.11 (146.07)	460.82 (220.79)	475.55 (142.27)	600.23 (110.46)				
0	RVIP false		8.37 (15.61)	7.47 (11.22)	7.68 (12.84)	7.13 (16.21)	6.50 (14.03)	19.62 (22.08)				
	Go/No go commission		10.89 (6.3)	9.00 (6.55)	10.47 (8.06)	9.20 (8.22)	9.47 (7.85)	13.08 (7.00)				
	Go/No go omission		11.06 (16.06)	18.72 (46.62)	29.21 (47.56)	24.73 (52.04)	36.53 (67.93)	20.82 (13.47)				
	Go/No go RT (ms)		387.23 (65.19)	376.37 (62.52)	406.15 (107.01)	396.74 (79.92)	442.93 (135.71)	394.01 (154.72)				
0	RVIP hits		13.88 (4.36)	13.88 (4.5)	16.27 (4.89)	16.29 (6.07)	17.09 (4.16)	6.41 (5.39)				
	RVIP latency (ms)		461.36 (98.83)	451.82 (139.91)	481.09 (156.83)	484.51 (188.95)	446.59 (123.12)	776.91 (252.43)				
	RVIP false		2.00 (2.19)	1.76 (1.82)	3.27 (5.91)	2.79 (2.94)	4.00 (3.95)	18.83 (20.90)				
	Go/No go commission		9.29 (5.00)	9.06 (5.58)	8.27 (5.34)	8.69 (5.69)	12.67 (7.48)	11.14 (3.64)				
0	Go/No go omission		7.79 (7.01)	18.24 (47.32)	23.73 (50.63)	21.38 (53.85)	13.22 (15.54)	27.78 (21.27)				
	Go/No go RT (ms)		425.09 (82.65)	419.20 (80.07)	438.69 (96.54)	413.17 (90.74)	384.66 (126.71)	358.02 (121.01)				

Note. Data are $M(SD)$. RVIP: Rapid Visual Information Processing; EMA: ecological momentary assessment.

TABLE 3
Results of linear mixed models for laboratory and field smoking behavior and cognitive performance data

	Group			Time			Group × Time										
	<i>n</i> ₁	<i>n</i> ₂	<i>df</i>	<i>PE</i> (16, 8 mg)	<i>SE</i> (16, 8 mg)	<i>F</i>	<i>P</i>	<i>df</i>	<i>PE</i>	<i>SE</i>	<i>F</i>	<i>P</i>	<i>df</i>	<i>PE</i> (16, 8 mg)	<i>SE</i> (16, 8 mg)	<i>F</i>	<i>P</i>
Lab data																	
Pleasure (1–7) ^a	387	55	2, 277	–0.05, –0.04	0.33, 0.34	0.01	0.99	1, 54	–0.15	0.03	19.78	<0.001	2, 277	0.15, 0.04	0.08, 0.08	1.82	0.16
Satisfaction (1–7) ^a	387	55	2, 277	–0.28, –0.19	0.40, 0.41	0.25	0.78	1, 54	–0.14	0.03	15.52	<0.001	2, 277	0.12, 0.05	0.09, 0.09	1.92	0.33
Smoking choice ^b	–	48	2, 45	2.15, 2.00	0.68, 0.72	5.74	0.006	–	–	–	–	–	–	–	–	–	–
No. cigs (diary)	201	58	2, 90	–1.36, 2.31	1.53, 1.58	3.12	0.05	1, 52	–0.32	0.08	15.47	<0.001	2, 90	–0.08, –0.03	0.21, 0.21	0.07	0.93
CO (PPM)	412	58	2, 296	–1.88, –0.12	0.96, 1.00	2.62	0.07	1, 57	–0.15	0.10	2.54	0.12	2, 296	–0.18, –0.01	0.24, 0.25	0.42	0.66
Cotinine (1–6)	207	57	2, 96	–0.43, –0.62	0.19, 0.20	5.20	0.007	1, 53	–0.03	0.02	1.73	0.19	2, 96	–0.03, 0.01	0.06, 0.06	0.28	0.76
RVIP hits	202	57	2, 92	0.93, 0.58	1.27, 1.30	0.27	0.77	1, 52	0.26	0.10	7.17	0.01	2, 92	0.02, –0.10	0.25, 0.25	0.16	0.85
RVIP latency (ms)	202	57	2, 92	–24.86, –16.26	35.54, 36.76	0.25	0.78	1, 52	–4.34	3.06	2.01	0.16	2, 92	–7.00, –2.47	7.85, 7.90	0.43	0.65
RVIP false	202	57	2, 92	1.64, 2.31	2.30, 2.39	0.49	0.62	1, 52	–0.11	0.17	0.42	0.52	2, 92	–0.53, –0.25	0.44, 0.44	0.74	0.48
Go/No go commission	182	53	2, 79	–1.42, 0.39	1.62, 1.66	0.82	0.44	1, 49	0.62	0.18	0.25	0.62	2, 79	–0.39, –0.18	0.47, 0.47	0.99	0.38
Go/No go omission	182	53	2, 79	18.21, 6.78	14.92, 14.92	0.79	0.46	1, 49	0.61	1.43	0.18	0.67	2, 79	3.55, 2.33	3.76, 3.84	0.45	0.64
Go/No go RT (ms)	162	51	2, 65	27.81, 7.07	21.54, 21.54	0.98	0.38	1, 45	3.01	2.83	1.13	0.29	2, 65	–0.55, 4.72	7.42, 7.39	0.36	0.70
Field data																	
Satisfaction (1–7) ^a	609	36	2, 572	0.45, 0.32	0.50, 0.50	0.41	0.67										
Pleasure (1–7) ^a	611	36	2, 574	0.49, 0.25	0.49, 0.48	0.50	0.61										
Recency past cig ^c (1–	646	39	2, 606	–0.04, 0.29	0.29, 0.29	0.98	0.38										
4)																	
RVIP hits	188	36	2, 151	4.25, 2.30	2.70, 2.64	1.27	0.28										
RVIP latency (ms)	179	33	2, 145	–73.68, –145.0	51.33, 51.00	4.26	0.02										
RVIP false	188	36	2, 151	11.45, 0.78	9.44, 9.28	1.19	0.31										
Go/No go commission	213	30	2, 182	1.53, 2.25	3.10, 2.96	0.29	0.75										
Go/No go omission	213	30	2, 182	2.80, –4.78	9.49, 8.88	0.58	0.56										
Go/No go RT (ms)	213	30	2, 181	8.06, 34.34	69.44, 66.87	0.18	0.84										

Note. All models include baseline values and cigarettes per day as level 2 covariates. n_1 = number of level 1 units, that is, assessments, visits, or days; n_2 = number of subjects (level two units). PE = (unstandardized) parameter estimate; SE = standard error from mixed model. Choice analyzed by analysis of covariance model. For lab data, Time reflects Visit Number. Three participants were missing

baseline data on the Satisfaction and Pleasure variables. There was no baseline assessment for the diary cigarettes and recency of past cigarette. Significant associations (i.e., $p < 0.05$) are identified in bold.
RVIP: Rapid Visual Information Processing.

^a Anchors for smoking satisfaction and pleasure scale for lab and field data were 1 = *not at all* and 7 = *extremely*.

^b Outcome measure for smoking choice task was the number of times an individual chose to smoke (vs. abstain to earn money).

^c Options for smoking recency were 1 = *No cigarettes in past 2 hr*, 2 = *Smoked cigarette within 2 hr*, 3 = *Smoked cigarette within 30 min*, and 4 = *Just smoked/Smoking now*.