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Original Investigation

Differences in Cognitive Task Performance, Reinforcement Enhancement, and Nicotine Dependence Between Menthol and Nonmenthol Cigarette Smokers

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Abstract

Introduction: Menthol has been shown to target similar brain regions and neural receptors as nicotine, yet the association between menthol cigarette use and cognitive performance remains unknown.

Aims and Methods: This study examined differences in cognitive task performance between menthol (MS) and nonmenthol (NMS) cigarette smokers after acute cigarette consumption. Sixty white and black and/or African American, nonabstinent, MS (n = 30) and NMS (n = 30) were assessed presmoking and postsmoking their preferred cigarette on four computerized tasks: Continuous Performance Task (CPT; alerting attention), N-Back Task (working memory), Finger Tapping Task (motor control), and Apple Picker Task (reinforcement enhancement). Self-reported nicotine dependence and objective smoking topography measures were also compared between groups.

Results: Initial unadjusted analyses showed a significant effect of cigarette type × time on CPT speed (p = .042), where MS improved while NMS group worsened in CPT speed after smoking. After controlling for baseline cigarette craving and cigarette nicotine levels, the effect of cigarette type × time for all cognitive outcomes was statistically nonsignificant (ps > .05). However, there remained a significant effect of cigarette type, where MS versus NMS had poorer CPT (p = .046) and N-Back Task accuracy (p = .006) but faster N-Back speed (p = .039). There were no statistically significant differences between groups on reinforcement enhancement, nicotine dependence, or smoking behavior outcomes (ps > .05).

Conclusions: Contrary to our hypotheses, results did not find a significant effect of cigarette type on the change in cognitive performance after acute smoking in nonabstinent smokers. Further studies are needed to clarify the specific pharmacological effects of nicotine and menthol on cognitive functioning.

Implications: The current study is the first to compare the potential enhancement of cognitive task performance after acute cigarette smoking between satiated menthol and nonmenthol cigarette

smokers. Study results suggest that acute menthol cigarette use may not enhance cognitive function above and beyond nonmenthol cigarettes to increase dependence among menthol smokers. However, the contribution of other psychological factors (eg, craving, mood) and cigarette characteristics (eg, nicotine content) may be involved in cognitive function enhancement to perpetuate dependence and smoking persistence for menthol smokers.

Introduction

The overall prevalence of conventional cigarette use in the United States continues to decrease,[1] yet the prevalence of menthol cigarette use among smokers remains high, particularly among minority populations.[2] Black and/or African American (AA) smokers are historically the largest consumers of menthol cigarettes in the United States, but preference for menthol cigarettes has also rapidly increased among ethnic and racial groups, with one-third to one-half of Hispanic, white, and Asian smokers preferring menthol cigarettes.[3] A recent meta-analysis study also found specific racial differences in the relationship between menthol cigarette use and nicotine dependence, where AA menthol cigarette smokers had lower odds of quitting smoking while no association was found among white menthol cigarette smokers.[4] With menthol's potential role in the initiation and sustainment of tobacco use,[5] the impact of menthol flavoring remains a continuing public health concern.

Menthol has a variety of interacting effects with nicotine to reinforce smoking behavior.[6] Nicotine serves both as a powerful primary (eg, directly sustaining smoking behavior) and secondary (eg, magnifying rewarding value of stimuli accompanying smoking) reinforcer through multiple neurobehavioral and psychosocial factors.[7] Nicotine stimulates neuronal nicotinic acetylcholine receptors (nAChRs) in numerous brain regions to promote cognitive enhancing effects (eg, improvements in motor functioning, attention, learning, and memory) even outside of withdrawal relief, which can further enhance secondary reinforcement by increasing attention to and learning of cues associated with tobacco use.[8,9] Menthol has also been shown to enhance nicotine reinforcement independent of any sensory effects during nicotine self-administration among rodents,[10] even with a low enough dose of menthol incapable of direct reinforcement.[11] Menthol has been shown to magnify nAChR desensitization by prolonging the time that the receptors remain in a desensitized state.[12,13] Menthol cigarette smokers have also shown greater α4β2 nAChR densities and upregulation compared to nonmenthol cigarette smokers based on positron emission tomography scanning.[14]

There are also distinct interactive neurobiological effects when administering menthol + nicotine compared to menthol or nicotine alone.[15] In mice, menthol + nicotine coadministration promoted significant increases in nAChR activation in the hippocampus, prefrontal cortex, and striatal areas and significantly enhanced expression of nAChR in the prefrontal cortex, compared to nicotine alone.[16] In rats, administration of menthol + nicotine also increased locomotor sensitization and functional connectivity compared to nicotine alone.[17] Menthol + nicotine administration also increased dopamine neuron excitability and nicotine reward-related behavior, while menthol alone suppressed dopamine neuron excitability and nicotine reward-related behavior.[18]

There is evidence among nonnicotine-based studies that menthol itself may enhance cognitive performance. For instance, peppermint oil has been shown to improve cognitive task performance (eg, attention, concentration, rapid discrimination, and overall quality of memory).[19–22] However, menthol's potential enhancement of cognitive performance in the context of cigarette smoking among humans has yet to be explored.[23] Understanding the effect of menthol cigarette use on cognitive performance could clarify the association between menthol cigarette use and increased nicotine dependence. Additionally, as nicotine withdrawal can produce fatigue and reduce cognitive and motivational processes,[24,25] understanding cognitive effects during satiation can have implications for the initiation, progression, and maintenance of nicotine dependence and smoking behavior.

Current Study

The current study investigated menthol's potential enhancement of cognitive performance and reinforcement in the context of cigarette smoking. We examined differences in performance on computerized tasks after acute cigarette consumption between satiated menthol and nonmenthol cigarette smokers. We also examined differences in reinforcement enhancement and nicotine dependence between menthol and nonmenthol cigarette smokers utilizing subjective and objective measures of nicotine dependence and reward. We hypothesized that menthol cigarette smokers, compared to the nonmenthol cigarette smokers, would demonstrate improved computerized cognitive task performance after acute smoking as well as elevated nicotine dependence and reinforcement enhancement. Lastly, because of racial differences in menthol cigarette use, we planned to explore potential differences between white and AA smokers across outcomes.

Materials and Methods

Participants

Participants were recruited from January 2018 through June 2019 in Chicago, IL, USA. Key eligibility criteria included smokers aged 25–60 years old to minimize the variability in smoking exposure and the impact of cognitive development or aging on cognition; self-identified race as white or AA; currently smoking at least five cigarettes a day for at least 1 year (verified by carbon monoxide [CO] breath sample of ≥5 parts per million); and no cognitive, visual, hearing, or motor impairments. Exclusion criteria included regular use of both cigarette types; daily use of other tobacco products other than cigarettes; current treatment or diagnosis for psychological disorders based on the Mini International Neuropsychiatric Interview for DSM-5; marijuana use within the last month and other illicit drug use within the last year; heavy alcohol use within the last month (men: >14 drinks per week, women: >7 drinks per week)[26]; regular use of medications known to cause cognition impairment[27]; and cognitive impairment per the Quick Mild Cognitive Impairment screen.[28] This research was approved by the Institutional Review Board of Northwestern University (IRB#:STU00206041).

Procedures

Interested individuals first completed a telephone prescreen, and eligible individuals were invited to attend one in-person study session. Participants were initially categorized by cigarette type group (ie, menthol vs. regular or nonmenthol) based on self-report at telephone prescreen, which was then confirmed in-person with their physical cigarette pack. As this study was specifically testing enhancement effects while satiated, participants were instructed to continue to smoke and consume caffeine normally before their session to prevent the influence of nicotine and caffeine withdrawal and related symptoms on cognitive performance. After completing informed consent and confirming study eligibility (eg, CO verification), participants completed self-report measures using Research Electronic Data Capture (REDCap) Version 7. Participants completed training trials to learn each computerized task prior to assessment to reduce practice effects. Participants were then assessed on each of the four computerized tasks, where task order was counterbalanced between participants using a balanced Latin square to prevent order effects. Following a presmoking CO measurement, participants were given 10 minutes to smoke one of their preferred cigarettes *ad libitum* in separate smoking room through a smoking topography device. Cigarette blinding and standardized smoking were not used to maximize generalizability to natural and preferred smoking behavior. Following smoking, participants repeated the CO measurement and each computerized task to assess for changes after smoking. Depending on enrollment period, participants were compensated with $50–75 in cash after completing the study.

Measures

Participant Characteristics

Participants self-reported demographic and smoking-related information and history (Table 1). We also recorded cigarette characteristics for each participant's preferred cigarette smoked (eg, brand, nicotine levels, and menthol levels).[29,30] Although participants were not abstinent from smoking, nicotine withdrawal and craving were assessed to account for potential confounding influences on cognitive task performance. Using the Minnesota Tobacco Withdrawal Scale, participants indicated how strongly they experienced withdrawal symptoms in the last 2 hours (range = 0–21) with higher scores indicating greater withdrawal symptoms. Participants also completed the Questionnaire on Smoking Urges-Brief Scale as a measure of craving (range = 10–70) with higher scores indicating greater urge to smoke. Using the Positive and Negative Affect Scale, participants reported current levels for each emotion (range = 10–50) with higher scores indicating higher levels of positive or negative affect on each respective subscale. Participants also reported on their typical use of major dietary sources of caffeine and whether consumption on the day of testing differed from normal use.

Computerized Performance Tasks

Three validated cognitive tasks, which have shown significant cognitive enhancement effects from smoking, were administered using the University of Pennsylvania Computerized Neuropsychological Test Battery.[31] Specifically, the Continuous Performance Task (CPT) as a measure of alerting attention, the N-Back Task as a measure of working memory, and the Finger Tapping Task as a measure of fine motor abilities.[31] During the CPT, participants responded with a button press whenever a seven-segment line display formed a number or letter. During the N-Back Task, participants were required to remember a series of random letters presented individually and responded with a button press when the letter shown is an "X" (0-back), same as the prior letter (1-back), or two letters prior (2-back). Outcome measures for both the CPT and N-Back Task were total number of true positive responses (accuracy) and median response time for true positive responses in milliseconds (speed). During the Finger Tapping Task, participants tapped as quickly as possible with their index finger on the space bar for 10 seconds with

Table 1. Participant Characteristics (Overall and by Cigarette Type)

	Overall (N = 60)	NMS (N = 30)	MS (N = 30)	F or x^2	p
Demographics					
Age (mean, SD)	43.8 (8.6)	44.6 (9.5)	42.93 (7.6)	0.54	.467
Sex (N, % female)	30 (50.0%)	16 (53.3%)	14 (46.7%)	0.27	.606
Race (N, % AA)	17 (28.3%)	1 (3.3%)	16 (53.3%)	18.5	<.001
Sexual orientation (N, % minority)	7 (11.7%)	3 (10.0%)	4 (13.3%)	0.16	.688
Marital status (N, % married)	21 (35.0%)	13 (43.4%)	8 (26.7%)	1.83	.176
Education (N, % GED or less)	19 (31.7%)	10 (33.3%)	9 (30.0%)	0.08	.781
Employment (N, % employed)	37 (61.7%)	17 (56.7%)	20 (66.7%)	0.64	.426
Income (N, % ≤ $50 000)	27 (45.0%)	10 (33.3%)	17 (56.7%)	3.30	.069
Cigarettes smoked/day (mean, SD)	14.9 (6.0)	15.8 (6.4)	14.0 (6.4)	1.36	.248
# of years smoking (mean, SD)	24.5 (9.9)	25.9 (10.1)	23.1 (9.7)	1.15	.289
Nicotine levels of preferred cigarette (mean, SD)	1.12 (0.27)	0.94 (0.27)	1.31 (0.1)	46.4	<.001
Menthol levels of preferred cigarette (mean, SD)	3.39 (2.4)	0.01 (0.01)	5.06 (0.5)	1235.1	<.001
Baseline measures					
MTWS withdrawal total (mean, SD)	2.2 (2.8)	2.2 (2.4)	2.1 (3.2)	0.02	.892
QSU craving total (mean, SD)	33.5 (14.9)	28.8 (12.7)	38.2 (15.6)	6.61	.013
PANAS positive affect (mean, SD)	29.9 (9.2)	26.9 (8.6)	32.9 (8.9)	6.96	.011
PANAS negative affect (mean, SD)	11.3 (2.4)	10.9 (1.1)	11.6 (3.2)	1.53	.221
Minutes since last cigarette smoked prior to session (mean, SD)	48.6 (97.6)	39.2 (41.2)	58.0 (132.3)	0.55	.460
# of caffeinated drinks per day (mean, SD)	2.55 (2.60)	2.62 (2.22)	2.47 (2.96)	0.05	.822
Caffeine use day of testing (N, % same as usual)	50 (83.3%)	27 (90.0%)	23 (76.7%)	1.92	.166

NMS = nonmenthol smoker; MS = menthol smoker; SD = standard deviation; AA = self-identified as black and/or African American; MTWS = Minnesota Tobacco Withdrawal Scale; QSU = Questionnaire on Smoking Urges-brief scale; PANAS = Positive and Negative Affect Schedule.

five trials per hand. The outcome measure for the Finger Tapping Task was the total number of taps across both hands.

The Apple Picker Task is a computerized task utilized to measure the acute reinforcement-enhancing effects of nicotine from cigarette smoking.[32–34] Participants used arrow keys on a keypad to move a cursor to search a field of tree images on a computer screen. Participants pressed a button to search each tree for an apple. When an apple was found, a tone sounded, and a symbol briefly lit up as feedback to signal that a unit of the designated reward (30 seconds of preferred music) was earned. Participants were free to work on the task for as long as they wanted to earn more music. The number of responses required to find an apple constituting the reinforcement schedule (progressive ratio of 50 with 32 responses required for first reward). The outcome measure for the Apple Picker Task was the total number of responses, with higher number of responses indicating increased reinforced responding.

Nicotine Dependence

Nicotine dependence was measured with the Fagerström Test for Cigarette Dependence (FTCD) (range = 0–10; ≤2 = very low or no dependence; 3–4 =low; 5 = medium; ≥6 = high dependence) and the Brief Wisconsin Inventory for Smoking Dependence Motives (WISDM) (range = 11–70) with higher scores indicating greater nicotine dependence.[35,36]

Carbon Monoxide Assessment

CO levels measured in parts per million (ppm) were obtained using a portable Vitalograph CO monitor. CO assessments were utilized to biochemically verify eligibility status as a smoker (≥5 ppm) and to obtain CO levels before and after *ad libitum* smoking.[37]

Smoking Topography

Smoking behavior during *ad libitum* smoking was recorded using a Clinical Research Support System (CReSS) device, which is a handheld device that captures real-time smoking behavior. Smoking topography outcome measures examined were the total number of puffs, mean puff volume (mL), mean puff duration (seconds), mean interpuff interval (seconds), and mean puff flow (mL/s).

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistical Version 26, at the nominal 0.05 type I error rate. Bonferroni adjustments were used to correct for multiple comparisons. Differences in demographic and baseline variables were examined using chi-square and one-way analysis of variances (ANOVAs) by cigarette type group (menthol [MS] vs. nonmenthol [NMS] cigarette smokers). Significantly skewed variables (ie, CPT accuracy, N-Back accuracy and speed, and smoking topography total puff count and average puff volume) were adjusted using natural logarithmic transformation. Separate repeated measures ANOVAs were used to compare changes in computerized task performance and CO measures from presmoking to postsmoking (within-subjects variable: time) by cigarette type (between-subjects variable: group). Differences between cigarette type groups for each self-report measure of nicotine dependence and smoking topography outcomes were analyzed using ANOVAs.

Regarding sample size, as no previous studies had tested the effect of menthol cigarette use on improvement in cognitive task performance after smoking, the current study focused on testing the cognitive enhancing effects after smoking between cigarette type groups (within-between effect). A meta-analysis conducted by Heishman et al.[31] on the enhancing effects of smoking or nicotine on cognitive functioning found medium effect sizes for fine motor and attention[38–40] and effect sizes ranging from small to large for working memory[39,41] in studies focused on smokers. Therefore, to achieve a small to medium sized effect (Cohen's d = 0.3) between MS and NMS groups with 95% power and an alpha of 0.05, we targeted a total sample size of 64 participants with 32 per cigarette type group. However, because of recruitment difficulties, study enrollment was completed at a total of 60 participants (30 MS and 30 NMS). Additionally, although study design had initially aimed to recruit equal samples of white versus AA smokers in both MS and NMS groups to examine potential racial differences, only 3 out of 1050 total individuals screened identified as an AA nonmenthol smoker. Therefore, we only conducted exploratory analyses on cognitive task performance and nicotine dependence outcomes examining potential racial differences among MS only because of relatively balanced groups (14 white, MS vs. 16 AA, MS).

Results

Participant Characteristics

A total of 60 participants (30 MS and 30 NMS) were recruited and completed the study. No statistically significant differences were observed between MS and NMS for the majority of demographic or smoking-related variables (Table 1). However, MS were more likely than the NMS to self-identify their race as AA. As expected, the preferred cigarettes smoked by MS and NMS differed statistically on menthol levels for their preferred cigarette, with cigarettes smoked by MS having higher menthol levels. However, the preferred cigarettes smoked by MS also had statistically significantly higher levels of nicotine. MS also reported statistically significantly higher levels of craving and positive affect at baseline compared to NMS, but there were no significant differences in level of withdrawal or negative affect at baseline between MS and NMS.

Computerized Performance Tasks

Computerized performance task outcomes from presmoking to postsmoking (within-subject: time) by cigarette type (between-subject: group) are presented in Figure 1. For the CPT accuracy, there was not a statistically significant interactive effect of time × group ($F(1,56) = 0.17$, $p = .69$). But there was a statistically significant effect of time ($F(1,56) = 25.06$, $p < .001$), where participants on average improved in CPT accuracy from presmoking to postsmoking. There was also a statistically significant between-subject effect of group ($F(1,56) = 5.33$, $p < .03$), where NMS smokers had higher CPT accuracy on average compared to MS. Notably, for CPT speed, there was a statistically significant effect of time × group ($F(1,56) = 4.33$, $p = .04$)—where MS improved in CPT speed (ie, response time decreased) from presmoking to postsmoking, while NMS worsened (ie, response time increased). There was not a statistically significant of time ($F(1,56) = 2.27$, $p = .14$) nor group ($F(1,56) = 1.04$, $p = .31$) on CPT speed.

For the N-Back Task outcomes, there was not a statistically significant effect of time × group on N-Back accuracy ($F(1,57) = 0.31$, $p = .58$). But there was a statistically significant effect of time ($F(1,57) = 5.05$, $p = .03$), where participants overall improved in N-Back Task accuracy from presmoking to postsmoking. There was

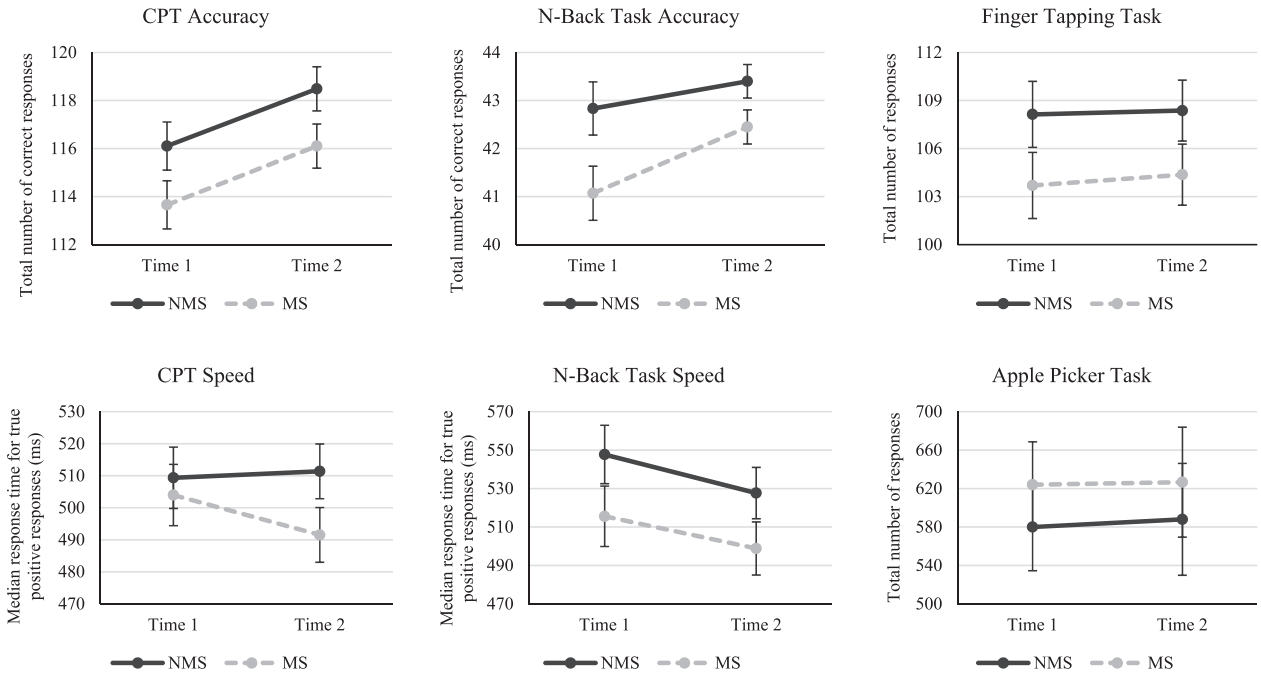

Figure 1. Mean (±SEM) for computerized task outcomes by timepoint by cigarette type group. *Note*: Mean values and standard error bars (SEM) for computerized task outcomes presmoking to postsmoking between nonmenthol cigarette (NMS) and menthol cigarette (MS) smokers. Means are adjusted for differences in nicotine level of preferred cigarette (nicotine) and baseline craving (craving). Better task performance is indicated by higher values for accuracy and lower values for speed for the Continuous Performance Task (CPT) and N-Back Tasks and higher values for the number of responses during Finger Tapping Task. Higher values for the number of responses during the Apple Picker Task indicate greater reinforced responding. CPT accuracy and N-Back Task accuracy and speed were log adjusted for skewness for analyses.

also a statistically significant effect of group ($F(1,57) = 7.75$, $p < .01$), where NMS smokers had higher N-Back Task accuracy compared to MS. Similarly, for N-Back Task speed, there was not a statistically significant effect of time × group ($F(1,56) = 0.01$, $p = .92$). But there was a statistically significant effect of time ($F(1,56) = 7.84$, $p = .01$), where on average participants improved in N-Back Task speed from presmoking to postsmoking. We did not find any statistically significant effects for Finger Tapping Task or Apple Picker Task outcomes ($ps > .05$).

Because of statistically significant differences in nicotine level of preferred cigarette (nicotine) and baseline craving (craving) between MS and NMS, both variables were then included as covariates in CPT and N-Back Task analyses to control for any potential effects on task performance. Regarding CPT accuracy, there was no longer a statistically significant effect of time after controlling for covariates ($F(1,54) = 1.05$, $p = .31$). Instead, there was a statistically significant effect of time × craving on CPT accuracy ($F(1,56) = 5.12$, $p = .03$). Specifically, participants who had reported lower levels of craving at baseline demonstrated a greater increase in CPT accuracy after smoking compared to participants who reported higher levels of craving at baseline. There remained a statistically significant between-subject effect of group on CPT accuracy after controlling for covariates ($F(1,54) = 4.18$, $p = .046$), where NMS still had higher CPT accuracy compared to MS. Regarding CPT speed, there was no longer a statistically significant effect of time × group ($F(1,54) = 1.64$, $p = .21$) nor time ($F(1,54) = .02$, $p = .80$) after controlling for covariates. However, there was a statistically significant effect of time × craving on CPT speed ($F(1,54) = 4.32$, $p = .04$). Specifically, participants who reported lower levels of craving at baseline improved in CPT speed after smoking, while participants who reported higher levels of craving at baseline worsened in CPT speed after smoking. There was not a statistically significant effect of group for CPT speed after controlling for covariates ($ps > .73$).

For N-Back Task accuracy, there was no longer a statistically significant effect of time after controlling for covariates ($F(1,55) = 1.81$, $p = .18$). Instead, there was a statistically significant effect of time × nicotine on N-Back Task accuracy ($F(1,55) = 4.91$, $p = .03$). Specifically, participants who smoked a cigarette with lower nicotine levels improved in N-Back Task accuracy after smoking, while individuals who smoked a cigarette with higher nicotine levels worsened in N-Back Task accuracy after smoking. There also remained a statistically significant between-subject effect of group on N-Back Task accuracy after controlling for covariates ($F(1,55) = 8.19$, $p = .01$), where NMS still had higher N-Back Task accuracy compared to MS. For N-Back Task speed, there was no longer a statistically significant effect of time ($F(1,54) = 1.43$, $p = .24$) nor any interactive effects ($ps > .15$) after controlling for covariates. However, there remained a statistically significant between-subject effect of group on N-Back Task speed after controlling for covariates ($F(1,54) = 4.48$, $p = .04$), where MS still had faster N-Back Task speed compared to NMS.

Nicotine Dependence and Smoking Topography

Mean scores for each nicotine dependence and smoking topography measure by cigarette type group are presented in Figure 2. There was not a statistically significant difference by cigarette type on the total scores for the FTCD or WISDM ($ps > .06$), nor for any of the CReSS smoking topography measurements ($ps > .20$). There was also not a statistically significant difference in the change of CO from presmoking to postsmoking between NMS and MS groups

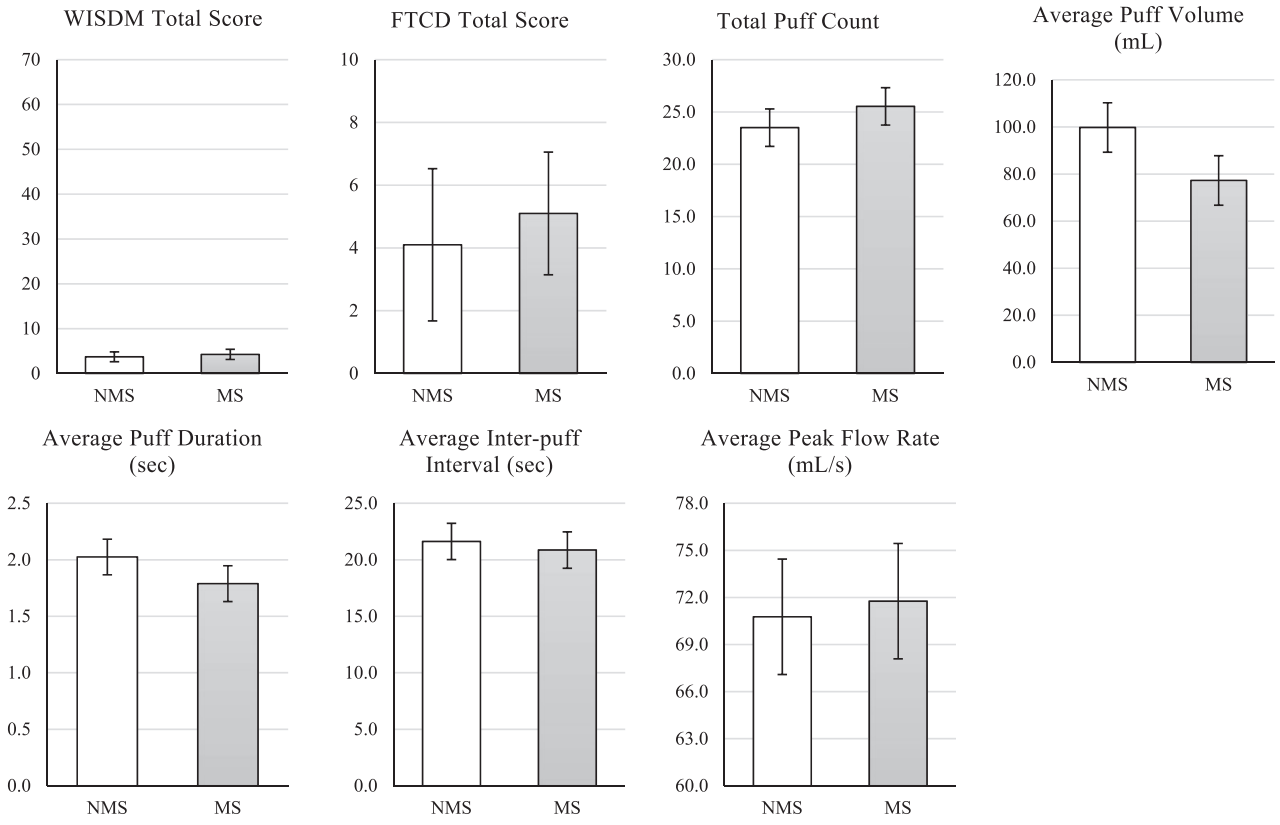

Figure 2. Mean (±SEM) nicotine dependence and smoking topography outcomes by cigarette type group. *Note*: Mean values and standard error bars (SEM) between nonmenthol cigarette (NMS) and menthol cigarette (MS) smokers. Smoking topography total puff count and average puff volume were log adjusted for skewness for analyses.

(mean [SD] = 18.5 [9.0] to 20.4 [8.6] vs. 16.8 [8.0] to 19.8 [8.0] ppm, respectively; $F(1,57) = 2.97$, $p = .09$).

Exploration of Racial Group Differences Among Menthol Smokers

Because of a lack of AA smokers in the NMS group, we explored potential differences between white and AA participants in the MS group only for each outcome. Regarding participant and baseline characteristics, the only statistically significant difference between white and AA smokers was the number of CPD smoked (mean [SD] = 16.7 [5.5] vs. 11.5 [4.3], respectively; $F(1,28) = 8.00$, $p = .01$), which was therefore controlled for in exploratory analyses. The only computerized cognitive task outcome that showed a statistically significant effect of time × race was CPT accuracy ($F(1,26) = 4.66$, $p = .04$), where white, MS had a greater increase in CPT accuracy after smoking compared AA, MS. There were no statistically significant differences by race for either nicotine dependence measure (ps > .39). Regarding smoking topography measures, the only statistically significant difference between white, MS and AA, MS was in the total number of puffs taken ($F(1,27) = 5.30$, $p = .03$), where white, MS took significantly fewer puffs while smoking compared to AA, MS (mean [SD] = 22.6 [10.4] vs. 28.1 [8.8], respectively).

Discussion

To our knowledge, the present study is the first study designed to explore the influence of acute menthol versus nonmenthol cigarette smoking on cognitive task performance in a human laboratory study. The study tested differences between cigarette type in three cognitive domains previously shown responsive to the acute effects of nicotine without the effects of nicotine withdrawal (ie, alerting attention, working memory, and fine motor skills). We also utilized a computerized task designed to test the reinforcement-enhancing effects of nicotine from cigarette smoking. We also examined differences between MS and NMS on self-reported nicotine dependence and objective smoking topography measures. The study also explored potential racial group differences, although difficulties in recruitment limited the examination to MS only.

Despite basic science evidence, results from the current study did not support study hypotheses that acute menthol cigarette smoking, compared with nonmenthol cigarette smoking, would be associated with a greater increase in cognitive task performance or reinforcement enhancement. Although initial unadjusted analyses did find significant interactive effect of group by time on CPT speed, there was no longer a significant effect of group by time for CPT speed after adjusting for covariates (ie, nicotine content of cigarettes and baseline craving). Initial unadjusted analyses also found significant within-subject effects of time on CPT accuracy and N-Back Task accuracy and speed, indicating a general improvement in performance after smoking. However, there was no longer a significant effect of time for any cognitive performance outcome after adjusting for covariates—potentially suggesting that there may be notable effects of nicotine content or craving on the improvements seen in cognitive task performance from smoking. While the current study aimed to focus on differences in the *change* in cognitive task performance

between MS and NMS (ie, time × group interaction), it should be noted that there was a significant between-subject effect of cigarette type group on CPT and N-Back Task outcomes, even after adjusting for covariates. Specifically, after adjusting for baseline craving and nicotine levels, MS had significantly lower accuracy on the CPT and N-Back Task, but significantly faster N-Back Task speed, compared to NMS. DeVito et al. also found no significant differences in the change in performance over time by cigarette type groups in response to I.V. nicotine, but MS had lower throughput scores (an overall performance score accounting for accuracy and speed) across all timepoints on both the Stroop Task and the Mathematical Processing Task compared to NMS.[42]

Broad or definitive conclusions about the effect of menthol versus nonmenthol cigarette use cannot be drawn as only CPT speed analyses had adequate power to detect a significant interactive effect. Post hoc analyses found that the current study was adequately powered (>80%) to detect significant smoking effects (ie, change across time) on across CPT and N-Back Task outcomes and had 75% power for the Finger Tapping Task. Notably, previous studies have been limited by small sample sizes and inadequate power.[31] The meta-analysis conducted by Heishman et al. found the average study sample size across reviewed studies was 24 (SD = 18) participants (with the majority of sample sizes being ≤20), resulting in only 14% of the studies being adequately powered to detect the estimated effect size.[31] Therefore, additional studies with larger sample sizes are needed to confirm and clarify enhancement of cognitive task performance across the various cognitive domains.

The effect of menthol cigarette use on cognitive task performance may also be more complex and harder to detect than indicated from basic science studies or studies examining essential oils. Basic science studies also differ in study methodology, including differences in the delivery methods and dosages of nicotine and menthol. For instance, menthol has been shown to increase oral, but not intravenous, nicotine consumption among rats.[43] Among rats, the addition of menthol to oral administration of nicotine also found a dose-dependent effect of menthol, where higher menthol doses induced significant decreases on subsequent reinstatement responding to nicotine after extinction.[44] The effect of peppermint on cognitive performance in human studies also differed based on whether the peppermint was ingested or inhaled.[45] As studies on peppermint essential oil found that the cognitive effects of menthol may potentially improve performance by reducing cognitive or mental fatigue,[22] it is also unclear how cognitive task performance may vary over longer periods of time with chronic menthol cigarette use.

Contrary to study hypotheses, the current study also did not find any differences between MS and NMS on any measurements of nicotine dependence or smoking behavior. Participants were required to be actively smoking and satiated to prevent effect of withdrawal and did not report high levels of craving or withdrawal at baseline. However, MS did report higher baseline craving and positive affect levels compared to NMS. Adjusted analyses also found a significant effect of baseline craving levels on CPT accuracy and speed outcomes. As variations in neuronal nAChR genes, which are affected by menthol, have been associated with differences in craving response,[46] MS may be more susceptible to poorer craving relief. Previous studies on craving relief from smoking also found that MS experience smaller decreases in reported craving levels from smoking compared to NMS,[42] suggesting that long-term exposure to menthol may change sensitivity to nicotine and potentially reduce withdrawal severity.[47] Similarly, alterations in nAChR signaling and response play a role in mood regulation and the presentation and treatment of various psychiatric and mood disorders,[48] potentially contributing to high prevalence of menthol cigarette use among individuals who report psychiatric disorders and symptoms.[49] However, it is unclear the role of positive affect in relation to acute or chronic menthol cigarette use, as studies have found negative affect instead to be more predictive of greater smoking motivation and poorer treatment outcomes.[50,51] Future studies examining the presentation of craving and affect between MS and NMS may help to clarify potential cognitive differences in response to nicotine and smoking.

Results should be considered in the context of study limitations. First, the study utilized a between-subject design in examining the effect of acute menthol cigarette smoking and did not control for nicotine or menthol intake. Participants may have received differing amounts of nicotine and menthol based on their preferred cigarette, smoking pattern, and when they had last smoked. Notably, there were no statistically significant differences between groups in the time since last cigarette smoked (Table 1), and outcomes did not differ when time since last cigarette smoked was included as a covariate in the models. Smokers also have a strong preference for their preferred brand and flavoring and manipulating the menthol content of cigarettes has been shown to influence subjective ratings of smoking and nicotine discrimination for MS.[52,53] Allowing participants to smoke their own preferred cigarette *ad libitum* exemplified the amount of cognitive enhancement obtained during normal smoking behavior. We were also able to compare differences in smoking topography outcomes between cigarette types, which would not be possible with prescribed smoking procedures. Furthermore, although we had originally intended to match groups on cigarette nicotine levels to reduce variability in nicotine consumptions, almost all MS (97%) smoked Newport cigarettes. Future studies incorporating standardized dosing of nicotine and menthol (eg, gum, patch, or intravenous nicotine and/or menthol dosing) may help to provide clarification of the specific pharmacological effects of nicotine and menthol on cognitive task performance. Second, as the current study was designed to focus on the acute enhancement effect of menthol cigarette smoking in a relatively healthy and nonabstinent sample, our findings may not be generalizable to smoking to specific populations (eg, risky alcohol users, polysubstance users, and individuals with mood symptoms), other flavored smoking or nicotine products (eg, e-cigarettes, noncombustible tobacco products), or because of smoking abstinence. Third, our smaller sample size also limited our ability to examine potential racial differences in cognitive performance. Although this study was unable to explore racial effects across both cigarette type groups, exploratory analyses among MS found that white smokers had a significantly greater increase in CPT accuracy from presmoking to postsmoking compared to AA smokers. Future studies should continue to strive to examine potential differences by race in the effects of menthol cigarette use on neurobiological mechanisms—although recruitment of NMS among AA smokers for balanced groups may be difficult.

Overall, study results did not find a significant effect of cigarette type on change in cognitive performance after acute smoking (time × cigarette type) after adjusting for the nicotine content of cigarettes and participant baseline craving levels. However, even after adjusting for covariates, there remained a significant between-subjects effect of cigarette type, where MS had lower accuracy during the CPT and N-Back Task but had faster speed during the N-Back Task compared to NMS. While replication is needed in a larger and sufficiently powered sample, the current study provided an initial examination

of the potential differences in cognitive task performance after acute cigarette smoking between satiated MS and NMS. Additional studies are also needed to clarify the effect of individual (eg, craving, mood)- and cigarette (eg, nicotine content)-related characteristics on menthol cigarette use and cognitive functioning. Understanding menthol flavoring continues to become more relevant in policy development, particularly as MS may be more likely to seek smoking cessation treatment as regulation policies continue to target the banning of menthol cigarettes. Clinical treatment targets could also be revealed and enhanced as research studies continue to specify and clarify the potential underlying neurobiological processes influenced by menthol cigarette use.

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Declaration of Interests

Dr Simon is a member of the US Preventive Services Task Force (USPSTF) and her written views do not necessarily reflect those of the Task Force. All other authors declared no potential conflicts of interest.

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