Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix

Methods

Participants

The primary inclusion criteria that participants must be willing to make a 3-day cessation attempt refers to the smoking abstinence requirement across the two R-E/NR-E training sessions and the 24-hr test session (carbon monoxide (CO)-verified). Participants were excluded if they were taking beta-blockers, anti-arrhythmic agents, psychostimulants, or any other agents known to interfere with heart rate or blood pressure, met diagnostic criteria for current/active (untreated) psychotic disorder, current major depressive disorder, bipolar affective disorder, or a severe anxiety disorder assessed with the Mini International Neuropsychiatric Interview (M.I.N.I.[1,2]), or met DSM-IV criteria for substance dependence (other than nicotine) within the past 60 days (assessed using the Substance Use Disorders section of the Structured Clinical Interview for DSM-IV Axis I Disorders; SCID-I[3]). To verify abstinence from substances other than cigarettes, participants had to produce a negative breathalyzer (alcohol) assessment and urine drug screen (benzodiazepines, methamphetamine, cocaine, marijuana, and opiates) on the day of the baseline smoking cue-reactivity assessment, two R-E/NR-E training sessions, and the 24-hr follow-up session.

Session measures

The four-item Craving Questionnaire (CQ[4]) assessed participants' craving "right now" on a scale from 1 (*strongly disagree*) to 5 (*strongly agree*). Items were: (1) "Nothing would be better than smoking a cigarette right now", (2) "I have an urge for a cigarette", (3) "All I want right now is a cigarette", and (4) "I crave a cigarette right now". Mood Form (MF[5]) items assessed negative affect "right now" on a scale from 0 (*not at all*) to 6 (*extremely*). Heart rate (HR) was collected via two electrodes, one affixed to the right shoulder and the other on the bottom left side of the participant's ribcage. Blood pressure (BP) was measured intermittently using a non-invasive inflatable arm cuff. Skin conductance was also assessed continuously during the first 50 s of cues presented, but collection error resulted in infeasibility in analyzing these data. The Timeline Follow-Back (TLFB[6]), used to assess baseline smoking behavior over the previous 2 weeks, is a calendar-based instrument that uses specific probes to ascertain detailed information about the quantity of use on a daily basis. Smoking variables were extracted from at-home smoking diaries participants completed in the 2 weeks prior to the 2-week and 1-month follow-up sessions.

Smoking stimuli

As indicated in Figure 1 (and consistent with Xue et al.[7]), smoking cues were presented in three formats—video, picture, and in vivo—during the two R-E/NR-E training sessions. The baseline session involved video cues only whereas the three follow-up test sessions (i.e., 24 hr., 2 weeks, and 1 month) involved exposure to both video smoking cues and a set of novel picture cues (e.g., picture of an ashtray, pack of cigarettes with a lighter; none of the picture cues presented in the test sessions had been presented in a previous session; pictures were obtained from Dr. Stephen Tiffany's research group). The 5-min video smoking cues consisted of 12, 30-s video segments depicting individuals of both sexes engaging in smoking-related behaviors (e.g., lighting up a cigarette and smoking). The craving and cue-reactivity potency of the smoking videos has been demonstrated in smokers[8]. Control videos (e.g., person reading a book) served as the neutral retrieval cue for participants assigned to Group NR-E. Picture cues in the R-E/NR-E training sessions consisted of a set of 30 smoking-related images (e.g., person exhaling cigarette smoke). The cue-reactivity potency of these cues among smokers has been documented in several publications[9-11]. Images were displayed on a computer monitor located directly in front of the participant. Each image was displayed for 8 s, with a 2-s delay between images (total approximate duration was 5 min). To assess whether the effects of R-E training generalized to novel smoking stimuli, participants were administered a brief "novel" smoking picture cue exposure sequence during each test session. The picture sequence occurred approximately 30 min after the video cues and consisted of 12 novel smoking pictures, presented for 8 s each (2-s delay between each). Procedures for in vivo cue observations are described in our previous study[12]. The duration of the in vivo cue experience was 5 min.

Procedure

Participants were consented upon arrival at MUSC for Session 1, and completed screening to determine eligibility (FTND, TLFB, M.I.N.I., SCID-I). Eligible participants were enrolled in the study by study staff and smoking abstinence was assessed using self-report verification followed by breath CO assessment. Consistent with previous research[13,14], participants were considered overnight abstinent if their breath CO level was ≤ 10 parts per million (ppm). Failure to meet abstinence requirements via breathalyzer or urine drug screen resulted in rescheduling.

Participants then completed a baseline smoking cue-reactivity assessment, the goal of which was to obtain pre-treatment estimates of reactivity to video cues with smoking content. Participants were seated in front of a computer monitor and the HR sensors and BP cuff were affixed. They remained seated for 10 min, after which 50 s

of continuous HR data were collected and participants completed the pre-cue CQ and MF, and had their BP assessed. Participants then completed the cue-reactivity procedure, with assessments of HR, CQ, MF, and BP collected throughout. Sensors were removed and participants received the scheduled compensation.

The two sessions of R-E/NR-E training were performed on consecutive days. Participants provided breath CO, UDS, and breathalyzer assessments upon arrival to MUSC to assess compliance with abstinence. If participants failed the abstinence assessment, they were rescheduled; if participants failed the abstinence assessment on the second day, however, they were dropped from the study. Pre-cue measures of craving and physiological reactivity were obtained and individuals in Group R-E watched the 5-min video with smoking-related content (same as seen during the baseline smoking cue-reactivity assessment) whereas individuals in Group NR-E viewed the 5-min control video with neutral, smoking-irrelevant content. This experimentally manipulated 5-min retrieval video (smoking vs. neutral) was the only way in which groups differed at any point in study procedures. The video presentation represented the putative memory retrieval feature of the study and, theoretically, should have initiated reconsolidation of memories for smoking-related learning in Group R-E, but not NR-E. Participants then engaged in a cue-reactivity/extinction procedure (Figure 1). At the completion of extinction training, the study coordinator removed the HR sensors and the BP cuff. Participants were reminded that they were being compensated (escalating schedule of compensation) to remain abstinent from smoking and other substances during the two R-E/NR-E training sessions and the 24-hr follow-up session.

Participants completed follow-up test sessions 24 hr, 2 weeks, and 1 month after the second R-E/NR-E training session (procedures at follow-up test sessions are depicted in Figure 1). Upon completion of the laboratory procedures, participants were compensated for their participation. Participants were compensated as follows: Screening, assessment, and baseline cue reactivity session=$60.00; R-E/NR-E training (Sessions 2 and 3)=$75.00 and 100.00, respectively; Session 4 (24-hr follow-up)=$125.00; Sessions 5 and 6 (2-week and 1-month follow-up)=$100.00 each. The maximum compensation for participation was $560.00.

Randomization

Urn variables of sex and level of nicotine dependence (Fagerström Test of Nicotine Dependence; FTND[15]) were used in stratified urn randomization as both variables are known to influence smoking cue-reactivity and behavior[16,17]. Co-author and statistician, Nathaniel Baker, generated the random allocation sequences and assigned participants to intervention groups.

Data management

Demographic and Clinical Characteristics. Summary values were computed from demographic and clinical measures obtained during the screening and diagnostic assessment. Continuous data are presented as means and standard deviations and are compared across treatment assignments using a t-test statistic (Table 1). Categorical data are presented as proportions and counts and were compared across treatment assignments using a normal chi-square test statistic. Additionally, baseline demographic and clinical characteristics were tested for univariate associations with study outcomes.

Outcomes. Means were calculated at baseline and post-cue presentation for the four craving items, five negative affect items, and HR data. Across the 14 days prior to the 2-week and 1-month follow-up sessions, average CPD and count of total number of days on which zero cigarettes were smoked were extracted. Additionally, we calculated the percentage of participants in each treatment group who had 50%, 60%, and 75% reduction in cigarettes from baseline to 2-week and 1-month follow-up. Smoking lapse was defined as latency to first cigarette, whereas smoking relapse was defined two ways: (i) latency to 7 consecutive days of smoking ('7-day criterion'), and (ii) latency to 3 consecutive days of smoking ≥5 cigarettes ('3-5 criterion'); both are considered milestones within cessation literature[18].

Primary outcomes analysis

Consistent with the proposed intent-to-treat analysis, we categorized all study participants based on their randomized treatment assignment for our primary and secondary statistical analysis. The primary study outcome of interest was the effect of R-E versus NR-E on craving and cue-reactivity at the 24-hr, 2-week, and 1-month post-treatment follow-up test sessions. Generalized linear models were developed to analyze treatment group differences in craving, negative affect, and physiological responses to the familiar and novel test session cues; additionally, tonic (i.e., non-cue elicited) levels of craving, negative affect, and physiological responses were assessed prior to any stimulus presentation. Within-subject measure correlations were modeled using multiple structures and final craving and physiological models were chosen to best fit the covariance structure without undue stress on available degrees of freedom (1st order autoregressive structure was chosen for craving and cue-reactivity models). Model-based estimates and associated standard errors were tabulated from the models and compared across treatment groups at each follow-up test session cue presentation. The models were developed such that contrasts (by treatment) at each of the 24-hr, 2-week, and 1-month follow-up sessions would be assessed and, when significant,

relevant pairwise comparisons would be made. Effect sizes are presented as Cohen's d (calculated using pooled standard deviation estimates). Adjusted models were developed using pre-treatment baseline measures of each outcome as well as covariates that evidenced association with the outcome measure or acted as a confounder. Any variables evidencing even a modest level of association with an outcome ($p<.20$) were included as initial covariates in the development of adjusted models. Models were developed using a stepwise additive process with a focus on reduction of bias in the final model estimates, reduction of collinearity among covariates, and model parsimony. In addition to the primary treatment effect analysis, the differential effect of treatment over time was tested using interaction terms in each outcome model (and then removed when found insignificant).

Smoking outcomes analysis

Smoking behavior was assessed using Timeline Follow-back (TLFB), expired carbon monoxide (CO), and urine cotinine (COT) at each study follow-up test session (smoking diaries were also used to assess smoking behavior (e.g., cigarettes per day; CPD) in between the 24-hr and 2-week and between the 2-week and 1-month follow-up sessions). The primary smoking outcomes of interest were effect of R-E versus NR-E on average CPD for the two weeks leading up to the 2-week and 1-month follow-up test sessions (only 2 measures per participant), as well as expired CO and urine COT. Generalized linear models were developed to analyze treatment group differences in the primary smoking study outcomes (mean CPD, CO, COT). All smoking outcome models were adjusted for baseline smoking behavior taken as the two-week average CPD prior to study screening and CO/COT measures taken at screening.

Although not powered to evaluate group differences in abstinence and abstinence-related milestones (lapse and relapse[18]), we preliminarily examined these secondary smoking outcomes. Latency to smoking relapse was investigated using Cox Proportional Hazard models where the beginning of the relapse risk period was noted as the first day following the abstinence period. Participants were followed until meeting relapse criteria or study dropout/completion. Latency results are presented as hazard ratios (HR) and associated 95% confidence intervals (CI). Pertaining to percent reduction in cigarettes from baseline to 2-week and 1-month follow-up (50%, 60%, and 75%), proportions were compared across treatment assignments using methods of generalized estimating equations with sandwich variance estimates. Results are presented as risk ratios (RR) and associated 95% CI. The number of days abstinent from cigarettes for each participant was calculated using smoking diary data and was compared between treatment groups using zero inflated Poisson regression models.

Additional analyses

All follow-up test session measures were examined for correlations using Spearman's rank order correlation coefficient. Study retention was examined as the proportion of study participants that were retained to study milestones (each follow-up test session) and these proportions were compared across study sessions using a Pearson Chi-Square test statistic. All study analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) and SPSS version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Models were noted as statistically significant with an uncorrected two-sided $p<.05$.

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