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Olfactory Cue-reactivity in Nicotine-Dependent Adult Smokers

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Abstract

Cue-elicited reactivity is a significant factor in relapse during smoking quit attempts. Previous research has focused primarily on visual smoking cues, with very limited research examining reactivity to olfactory triggers. Twenty-six adult, non-treatment seeking, nicotine-dependent smokers were exposed to seven odorants during a cue-reactivity session measuring heart rate, skin conductance, and subjective craving. Cues included 2 cigarette odors (fresh tobacco and cigarette smoke), 2 odors previously identified as smoking-related (freshly mowed grass and coffee), 2 odors previously identified as unrelated to smoking (lavender and burned rubber), and 1 odorless control (propylene glycol). Pairwise comparisons demonstrated that subjective intensity of craving was significantly higher following exposure to the fresh tobacco odor compared to the odorless control ($p < .01$). A significant main effect for cue type on a physiological measure of arousal was also revealed, with a fresh tobacco odor-elicited significant increase in skin conductance level compared to the odorless control. No main effect of cue type on heart rate, however, was found ($p = .25$). The results of the present study indicate that cigarette odor is an effective olfactory cue that heightens both subjective craving and increases skin conductance in smokers. Future research is needed to evaluate whether avoidance of these odors, or extinction of responses to them, can reduce relapse risk during smoking quit attempts.

Keywords

Smoking; Odor cues; Craving; Tobacco dependence; Cue-reactivity

Cue-reactivity—the array of psychological, physiological, and behavioral effects elicited by drug-related stimuli — is a well-established paradigm to investigate craving that generally describes a greater response to drug-related, compared to neutral, cues in drug-dependent individuals (Drobes & Tiffany, 1997; Carter & Tiffany, 1999). While visual cues (e.g. picture of a lit cigarette) have been utilized most often in smoking cue-reactivity studies, a range of cues, across multiple modalities, have been shown to elicit conditioned reactions including handling a cigarette, the sound and feel of the flick of the lighter, being in close proximity to a person smoking, as well as script-guided imagery (Carter & Tiffany, 1999;

McRobbie et al., 2008, Erbllich & Bovbjerg, 2004). Contextual cues related to where people smoke, as well as behaviors that may coincide with smoking (e.g. drinking coffee/alcohol, driving a car, etc.) may also be effective conditioned stimuli (Paris et al. 2011; Conklin et al., 2010; Van Gucht et al., 2010).

Odors are among the most salient conditioning cues in the laboratory and natural environment (Paschall & Davis, 2002; Gagliardo, 2013), possessing the ability to overshadow cues presented to other sensory modalities (Taukulis & George, 1982). It is therefore quite surprising that very few investigations have specifically focused on the role of odors in drug cue-reactivity. However, a small but consistent literature has emerged from the alcohol field revealing that odor cues readily elicit craving and the associated physiological responses (Bordnick et al., 2008; Kareken et al., 2004), including increases in urge to consume alcohol, heart rate, and skin conductance level in alcohol-dependent, but not non-problem, drinkers (Rubonis et al., 1994; Kaplan et al., 1994; Stormark et al., 1995).

While numerous in-vivo smoking cue-reactivity studies (LaRowe et al., 2007; Carpenter et al., 2014; Niaura et al., 1998) have utilized smoking odors as a component of their multi-sensory drug cues, none have been able to isolate the sole impact of the odor component in their analyses. In fact, only two studies have attempted to specifically test whether cigarette odors are a relevant factor in smoking cue-reactivity, and both of those studies utilized just one odor, that of cigarette smoke (Ordonana et al., 2012; Grusser et al., 2000). There were additional limitations as well, including not providing a pure uni-sensory odor cue (Ordonana et al., 2012) and reporting subjective craving alone, with no objective measure of cue-reactivity (Grusser et al., 2000). Given that the role of odor cues in addiction, and in nicotine dependence in particular, is relatively less explored and understood compared to the impact of other cues (visual, multi-sensory 'in-vivo'), both subjective and objective measures of craving are warranted.

Targeting the olfactory system with the use of odor cues may contribute more real-world factors during studies of drug cue-reactivity. And, our methods could help to identify individual smokers who react to the smell of cigarettes, as well as other odors that have been conditioned to their smoking behavior. Ultimately this line of investigation may help to develop specific strategies to address during a smoking quit attempt. Therefore, the present study utilized cigarette odors, as well as smoking-related and neutral odors previously identified by our laboratory (Hartwell et al., 2012), to evaluate odor cue-reactivity in nicotine-dependent, adult smokers. Based upon previous findings in both nicotine- and alcohol-dependence (Ordonana et al., 2012; Grusser et al., 2000; Kaplan et al., 1985; Rubonis et al., 1994; Stormark et al., 1995), we hypothesized that cigarette and smoking-related, but not neutral, odor cues would elicit increases in skin conductance level (SCL), heart rate (HR), and subjective craving to smoke.

Methods

Participants

Adult smokers ($n=26$), between the ages of 18 and 59, were recruited through local advertisement. Study eligibility required potential participants to 1) smoke at least 10

cigarettes per day (menthol were included but other tobacco products were excluded), 2) be non-treatment-seeking or not in active smoking cessation treatment, 3) report no current or lifetime substance dependence, or past 30-day abuse, of drugs other than caffeine and nicotine, 4) be daily coffee drinkers who reported commonly smoking cigarettes while drinking their morning coffee (i.e. associated coffee and cigarettes), 5) have no current/past history of significant psychiatric illness, and 6) have no major medical problems, including no known problems with sense of smell. A confidential phone screen provided initial eligibility. Once IRB-approved informed consent was obtained, study eligibility was confirmed with 1) a detailed tobacco history, the Fagerstrom Test for Nicotine Dependence (FTND; Fagerstrom, 1978; Heatherton et al., 1991), and a breath carbon monoxide (CO) level 10 ppm (Bedfont Scientific Ltd, Kent, England), 2) urine drug (Wan Han Pu Man Inc., Irwindale, CA) and breath alcohol (Intoximeters, Inc., St. Louis, MO) screens, 3) Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), and 4) a medical examination and the University of Pennsylvania Smell Identification Test (UPSIT; Doty et al., 1984), a self-administered, 40-item, scratch-and-sniff test used to confirm normosmia, a normal sense of smell. Those that met all study criteria were scheduled for the laboratory study and instructed to remain abstinent from cigarettes for 12-hours before that scheduled time.

Laboratory Olfactory Cue Reactivity Paradigm

Odor cues—A total of seven odor cues, including 2 cigarette odors, 2 smoking-related odors, 2 odors unrelated to smoking, and 1 odorless control, were utilized in the cue-reactivity session. The odor cues were previously identified through a series of focus groups conducted prior to the start of the present study (Hartwell, et al., 2012). Fresh tobacco (TOB) and cigarette smoke (CIG), served as the cigarette odors, while two odors identified as commonly associated with smoking, freshly mowed grass (GR) and coffee (COF), served as the “smoking-related” cues. The 2 “unrelated” odors, identified as odors not related to smoking, included lavender (LAV), a pleasant odor, and burned rubber (BR), a relatively unpleasant odor. Propylene glycol (PG) was utilized as the odorless control, as well as the base oil for preparing other odor cues.

Nature slideshows—All slideshows consisted of high resolution, colored, nature scenes, each presented at 5-second intervals. A ten-minute slideshow was presented during the initial habituation period, while six, 3-minute, slideshows were presented between odor cues to reduce carryover effects from the previous cue.

Craving measures—Subjective reports for craving were assessed on 11-point analog scales measuring 3 aspects of craving: Analog scale #1 measured craving amount (0=very little, 10=a great deal); Analog scale #2 measured craving intensity (0=none, 10=irresistible); and analog scale #3 measured craving control (0=no control, 10=complete control).

Physiological measures—Heart rate (HR) and skin conductance level (SCL) data were obtained with the MP150 data acquisition system and AcqKnowledge 4.1 software for

windows (BIOPAC Systems, Inc., Goleta, CA) according to methods described by LaRowe et al., (2007).

Cue-reactivity procedure—On the day of testing, 12-hour smoking abstinence ($CO < 10$ ppm; Piper et al., 2009, Jorenby et al., 2006) was first confirmed, with participants not meeting this criteria rescheduled. Cue-reactivity was carried out in a dimly-lit, climate-controlled, air-filtered, testing room, with an adjacent control/monitoring room. Each 1 hour session was conducted using Superlab 4 (Cedrus Corp., San Pedro, CA), stimulus presentation software that turned the physiological recording equipment and slideshows on/off from the control room, as well as delivered all pre-recorded instructions, ensuring consistent odor sampling across all participants and odors. The session began with a 10-minute habituation period/slideshow after which 90s of baseline HR and SCL, as well as baseline craving, was acquired. Next, a study assistant briefly entered the room, retrieved the baseline measures, delivered the first odor flask and craving measures for that odor, then exited before the automated instructions for sampling the odor and SCL/HR data acquisition began. Odor sampling required participants to pick up the flask, place it under their nose, breathe through their nose 4 times on a 6-second breathing cycle, then replace the flask on the table. Once odor sampling, data acquisition, and craving measures were complete, the study assistant briefly re-entered the room to remove all items. Next, 3 minutes of nature slides were presented and the entire sequence of events was repeated starting with baseline HR and SCL for the next odor, until all 7 odors were sampled. All odors were presented in a counterbalanced design to offset order effects.

Statistical Analysis Strategy

All analyses were conducted using SPSS 22.0 (SPSS IBM, New York, US). The study design provided one within-subjects factor: cue type (TOB, CIG, GR, COF, LAV, BR, and PG), and five dependent measures: Amount of Craving, Intensity of Craving, Control over Craving, Mean SCL, and Mean HR. According to previously published methods (Gray et al., 2011), post-cue values of craving, SCL, and HR, were evaluated by subtracting pre-cue baseline values, providing difference scores. Repeated measures ANCOVAs were then performed separately for each dependent measure (craving items, SCL, and HR) with cue type as the within subjects variable, and nicotine dependence (FTND score), centered to the overall mean, as the covariate (Watson et al., 2010; Vollstadt-Klein et al., 2011; Jasinska et al., 2014). Pairwise comparisons were utilized to assess differential responses of each odor relative only to PG, the odorless control. Effect sizes were calculated using Cohen's d statistic (Cohen, 1988). In an attempt to reduce Type-I error, additional odor to odor comparisons were not considered. Secondary exploratory analyses utilizing independent-samples t -tests were conducted to determine if participant factors including sex or preferred cigarette (regular versus menthol) influenced craving ratings, HR, or SCL responses to the TOB or CIG odors.

Results

Participants

The twenty-six study participants were predominantly male (male=17, female=9), white (white=21, African American=3, Asian=1, other=1), between the age of 18 and 57 ($M=31.3$, $SD=10.36$), attended at least some college (62%), smoked an average of 17 cigarettes/day ($SD=6.6$, range=10–36) for an average of 14 years ($SD=10.2$, range=2–45), and had a mean FTND score of 5.4 ($SD=1.63$, range=2–8). Fifty-four percent of the group smoked menthol cigarettes. All participants had a normal sense of smell (UPSIT: $M=36.6$, $SD=1.4$, range=35–40).

Subjective Craving

Baseline ratings for each aspect of craving were relatively high (amount: $M=7.4$, $SD=2.6$; intensity: $M=6.6$, $SD=2.8$; and control: $M=7.0$, $SD=3.2$). ANCOVA revealed a statistically significant main effect of cue type on baseline-corrected craving intensity ($F_{6,24}=2.46$, $p=.027$), with a significant increase following TOB ($M=7.3$, $SD=2.9$) compared to PG ($M=6.1$, $SD=2.9$, $p=.002$). An increase in craving intensity that approached statistical significance was also found following CIG ($M=6.7$, $SD=2.8$) relative to PG ($p=.077$). No differences in post-cue ratings for the other odors were noted. Also, no main effect of odor on the other aspects of craving were revealed [amount of craving, ($p=.46$), and control over craving ($p=.40$)]. The main effect of the covariate, as well as its interaction with cue type, was non-significant.

Skin Conductance

SCL analysis revealed a significant main effect of cue type on baseline-corrected post-cue values ($F_{6,24}=2.13$, $p=.05$), with a significant increase in TOB-elicited SCL ($p=.035$; see Figure 1) but no significant change in SCL for the other odors relative to PG (see Table 1). As with subjective craving, the main effect and interaction of the covariate was non-significant.

Heart Rate

HR analysis revealed no main effect of cue type on baseline-corrected post-cue values ($F_{6,24}=1.33$, $p=.25$). As with previous analyses, the covariate was non-significant.

Secondary Exploratory Analyses

There were no differences in subjective craving, HR, or SCL between male and female participants, or between participants who smoked regular and those that smoked menthol cigarettes in response to the TOB or CIG odor cues.

Discussion

Results of this preliminary study demonstrated the ability of fresh tobacco odor to elicit an increase in skin conductance, as well as craving intensity, in 12-hour abstinent, nicotine-dependent adults. These findings are consistent with other cue-reactivity studies that utilized visual or in-vivo, multi-sensory, smoking cues (Drobes & Tiffany, 1997; Ordonana, et al.,

2012; Saladin et al., 2012; Niaura et al., 1998). Although Ordonana and colleagues (2012) previously reported an odor-elicited increase in skin conductance and heart rate in response to actual tobacco smoke, they also utilized visual smoking cues. And despite efforts to eliminate any long-lasting autonomic effects of the pictures, it is impossible to rule out potential interactions, or a priming effect, of the visual stimuli on the odor cue. Given Jasinska and colleague's (2014) suggestion that multi-sensory drug cues elicit greater responses than uni-sensory cues, the present study was required to determine the independent role of cigarette odor in smoking cue-reactivity, and thus the first to demonstrate that an isolated (i.e. uni-sensory) smoking odor cue is sufficient to increase both a subjective (intensity) and objective (SCL) measure of craving.

Although measures regarding hedonic value and ease of identification of the odors, as well as how closely the smoking odors resembled participants' preferred brand of cigarettes were not collected in the present study, the hedonic value of the odor cues was collected from smokers participating in focus groups held prior to this study (Hartwell et al., 2012). Those smokers rated fresh tobacco (TOB) as generally pleasant and cigarette smoke (CIG) as generally unpleasant. In the present study, both of these cigarette odors demonstrated the ability to elicit craving, albeit CIG at a level that approached statistical significance. This result is important to highlight given the findings of McRobbie et al. (2008) who reported that the hedonic value placed on the smell of another person's cigarette smoke was not a primary factor related to craving or relapse, but that finding that smoke "tempting" was, for smokers during a quit attempt. Taken together with the current findings, these data suggest that hedonic value placed on second-hand smoke may not be the best indicator of a smoker's desire, physiological response, or likelihood to smoke.

This is the first study to assess odors associated with behaviors that smokers commonly engage in while smoking (i.e. drinking coffee and being outdoors). While participants demonstrated cue-reactivity to TOB, there was a lack of effects for the smoking-related scents (COF and GR). While it is possible that COF and GR may not be as potent cues as the actual cigarette odors, these odors are to some degree personalized which could further limit their ability to demonstrate an effect (for a discussion on individualization as a factor in drug cue-reactivity see Jasinska et al., 2014). For example, despite the fact that our smokers were daily coffee drinkers who reported commonly smoking cigarettes while drinking their morning coffee, they may have consumed coffee or smoked independently during other times of the day. If these behaviors were not tightly paired, cue-reactivity to coffee odors would be less likely. Similar individualization of conditioned responses could have existed for those who smoked menthol versus non-menthol cigarettes. This does not seem to be the case however, as over half of our sample who regularly smoked menthol cigarettes demonstrated similar responses to the non-menthol-prepared cigarette odor cues as those who exclusively smoked non-menthol cigarettes.

While fresh tobacco odor significantly increased subjective 'intensity of craving', odor-induced increases in 'amount of craving' and 'control over craving' were not demonstrated. Given our 12-hour abstinent requirement, participants arrived to the laboratory already in a high state of craving. While the lack of a cue-induced increase in the "amount of craving" could be due, in part, to a ceiling effect, the results also suggest that the subjective report of

“craving intensity” may be a better index of the overall craving experience under an abstinence-induced high craving state. A main effect of cue type on heart rate was also not demonstrated. While the majority of cue exposure studies, regardless of drug class, have reported cue-elicited increases in heart rate, effect sizes are generally smaller than that for subjective craving and skin conductance (Carter & Tiffany, 1999). Interestingly, the largest effect size found in the present study was for the CIG-elicited increase in heart rate ($d = .41$; see Table 1), with a nearly comparable effect size for TOB ($d = .33$; see Table 1). However, effect sizes for LAV and BR, odors not related to smoking that did not elicit subjective craving, were also similar ($d = .34$, $d = .33$, respectively; see Table 1). These results suggest a general, rather than drug specific, effect of odor on heart rate.

The main limitation of the present study relates to the small sample size and the numerous odors tested, reducing the power to detect significant differences. For example, while a significant main effect of cue type on skin conductance was demonstrated, the reported cue-elicited increase for TOB did not survive a correction for multiple odor comparisons. Another limitation concerns our exclusion of participants with poor olfactory function. Given that dose and duration (i.e. pack-years) of cigarette smoking is negatively related to olfactory function (Frye et al., 1990), we may have truncated the sample by eliminating the smokers who smoked the most/longest, and in turn excluded those with significant smoking-cued responses. Moreover, because smoking-related olfactory deficits are reversible (Frye et al., 1990), it is possible that smoking odor cue-reactivity could increase over the course of longer-term abstinence. These questions remain for future investigations.

While preliminary, the present findings add to the existing body of literature by isolating odor cues and demonstrating their relevance in cue-reactivity, a finding previously reported in alcohol dependence but missing from the smoking literature. These findings also highlight the potential clinical importance of olfactory triggers. Our clinical experience suggests that some patients recognize independently that cigarette odors trigger their desire to smoke, while others require questioning to appreciate this relationship. If practicing clinicians fail to solicit information regarding olfactory triggers, they may miss the opportunity during the planning phase of a quit attempt to help patients develop strategies to avoid and/or cope with odor triggers. As the majority of quit attempts end in relapse, identification of previously less appreciated cues to smoke (i.e. odors) has the potential to enhance treatment outcomes. While further investigation regarding the role of odor cues in nicotine dependence is warranted, adding a non-smoking, between subjects comparison could determine if this cue-reactivity is specific to smokers. Future studies may also confirm the need for individualization of specific odors associated with the most common smoking environments for each smoker (Conklin, et al., 2010). This proof of concept study demonstrates that odor cues provide a new method to study smoking cue-reactivity and supports the use of odors to further research efforts in cigarette addiction.

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Figure 1.

Odor-elicited changes in skin conductance (SC). The graph depicts a difference score (post-cue SC minus pre-cue SC) for each odor; PG=propylene glycol, BR=burned rubber, COF=coffee, LAV=lavender, GR=freshly mowed grass, CIG=cigarette smoke, TOB=fresh tobacco. The * indicates a significant increase in baseline-corrected SC compared to PG ($p<0.05$).

Table 1

Effect sizes (Cohen's *d*) for odor-elicited changes in skin conductance and heart rate.

Odor	Odor- elicited change in SC			Odor-elicited change in HR		
	Mean (SD)	t (p-value) (compared to PG)	Cohen's <i>d</i> (compared to PG)	Mean (SD)	t (p-value) (compared to PG)	Cohen's <i>d</i> (compared to PG)
PG	0.80 (1.00)			0.36 (6.26)		
TOB	1.22 (1.52)	2.23 (.04)	.33	2.81 (8.30)	1.24 (n.s.)	.33
CIG	1.07 (1.48)	1.20 (n.s.)	.21	2.94 (6.19)	2.29 (0.03)	.41
COF	0.64 (1.20)	-0.68 (n.s.)	.16	0.12 (5.87)	-0.18 (n.s.)	.04
LAV	0.62 (0.98)	-0.96 (n.s.)	.18	2.39 (5.60)	1.41 (n.s.)	.34
GR	0.79 (1.14)	-0.09 (n.s.)	.01	0.71 (8.26)	0.18 (n.s.)	.05
BR	0.79 (9.22)	-0.06 (n.s.)	.01	2.43 (6.20)	1.86 (n.s.)	.33

SC=skin conductance, HR=heart rate, Mean=difference score (post-cue minus pre-cue) for each odor, PG=propylene glycol, BR=burned rubber, COF=coffee, LAV=lavender, GR=freshly mowed grass, CIG=cigarette smoke, TOB=fresh tobacco; n.s.= $p > .05$