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Preliminary test of cigarette nicotine discrimination threshold in non-dependent versus dependent smokers

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ABSTRACT

Background: Despite its potential for understanding tobacco dependence, behavioral discrimination of nicotine via smoking has not been formally examined as a function of nicotine dependence level.

Methods: Spectrum research cigarettes were used to compare non-dependent with dependent smokers on the lowest content of nicotine they could discriminate (i.e., "threshold"). Dependent (n = 21; 16 M, 5 F) or non-dependent (n = 7; 4 M, 3 F) smokers were tested on ability to discriminate between cigarettes with nicotine contents of 17, 11, 5, 2, and 1 mg/g, one per session, from an "ultra-low" cigarette with 0.4 mg/g (all had 9–10 mg "tar"). All abstained from smoking overnight prior to sessions, and number of sessions was determined by the lowest nicotine content they could reliably discriminate from the ultra-low on > 80% of trials (i.e., ≥5 of 6). Subjective perceptions and cigarette choice behavior were also assessed and related to discrimination behavior.

Results: Discrimination thresholds (and most perceptions) did not differ between dependent and non-dependent smokers, with median thresholds of 11 mg/g for both subgroups. Yet, "liking" and puff choice for threshold cigarettes were greater in dependent but not non-dependent smokers, while cigarettes with nicotine contents below threshold did not support "liking" or choice in both groups.

Conclusions: In sum, this preliminary study suggests threshold for discriminating nicotine via smoking may not vary by dependence level, and further study is needed to confirm that cigarettes unable to be discriminated are also not reinforcing.

1. Introduction

Because nicotine intake is critical to tobacco smoking (Stolerman and Jarvis, 1995; USDHHS, 2010), it appears unlikely that a low-nicotine cigarette that smokers could not discriminate (i.e., "feel the effects") from one virtually lacking in nicotine would support onset and maintenance of dependence (e.g., Kessler, 1994; Slade et al., 1995; Wayne and Carpenter, 2009). For this reason, cigarettes with nicotine content just above this amount, the minimum discriminable nicotine in tobacco (or "threshold"), likely have implications for public policy to reduce dependence risk (Hatsukami et al., 2010; Henningfield et al., 1998; Sofuoglu and LeSage, 2012). Specifically, the 2009 Tobacco Control Act allows FDA to regulate the nicotine content of tobacco products (U.S. Govt, 2009). Therefore, restricting nicotine content in commercial cigarettes below this discrimination threshold could result in a maximum nicotine exposure from smoking that is inadequate for dependence onset or maintenance (Benowitz and Henningfield, 1994). With such regulation, anyone not already dependent may never become dependent, and dependent smokers might more easily quit.

As with all drugs (e.g., Bolin et al., 2016; Glennon and Young, 2011; Johanson, 1991), behavioral nicotine discrimination testing involves identifying if one dose of nicotine can be reliably detected from an identically-appearing substance containing a lower dose, or no nicotine. Nicotine discrimination testing has a long history with non-human animals (Smith and Stolerman, 2009) but not with humans (Perkins, 2009). Limited human study is due primarily to lack of control over nicotine dosing via tobacco smoking, as dose exposure can vary widely if smoking topography varies (Benowitz et al., 1983). Until recently, just a few discrimination studies in humans involved nicotine administration, and all controlled dosing by means other than tobacco smoking (nasal spray, see Perkins, 2011; or oral capsules in Duke et al., 2015).

However, Spectrum research cigarettes (from the National Institute on Drug Abuse) are specifically engineered to provide a narrow range of nicotine contents, with different versions available down to very low amounts (see Donny et al., 2015). In contrast with commercial brands,

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these research cigarettes essentially prevent smokers from obtaining nicotine exposure different from the cigarette's contents by altering their puff topography (see Hatsukami et al., 2013; Marian et al., 2009). Using Spectrum cigarettes, we adapted methods from our prior studies on nicotine discrimination with nasal spray (reviewed in Perkins, 2011) to develop procedures testing nicotine discrimination via cigarette smoking (Perkins et al., 2016a). Subsequently, we evaluated procedures for determining the threshold "dose" for discriminating nicotine in dependent smokers (Perkins et al., 2016b), followed by comparison of dependent smokers who preferred menthol vs. non-menthol cigarette brands (Perkins et al., 2017).

In the current study, we compared cigarette nicotine discrimination threshold between dependent and non-dependent smokers (i.e., those not meeting DSM criteria for dependence) to explore whether threshold may differ due to dependence. Low doses may be discriminable in non-dependent smokers but not discriminable in dependent smokers, reflecting their possibly higher threshold. Alternatively, based on our nasal spray nicotine discrimination threshold research with smokers and nonsmokers (Perkins et al., 2001), presence of dependence may not matter as both may be able to reliably discriminate the same nicotine doses via cigarettes. In any case, formal test of nicotine discrimination in humans differing in level of dependence may be needed to determine a discrimination threshold for all who would have access to those cigarettes.

Finally, similar to other drug discrimination research with humans (e.g., Johanson, 1991), secondary analyses also examined associations of nicotine discrimination behavior with concomitant subjective perceptions and subsequent choice behavior in response to these cigarettes. One goal here was to explore the notion that a cigarette with nicotine contents too low to be discriminated from one virtually lacking in nicotine would also be too low to support acute smoking reinforcement (i.e., choice).

2. Material and methods

2.1. Participants

Eligible were dependent (n = 21; 16 M, 5 F) and non-dependent (n = 7; 4 M, 3 F) smokers who preferred non-menthol cigarettes. (All compared here were those preferring non-menthol due to very few non-dependent menthol smokers available for testing; other research directly compares nicotine discrimination based on menthol preference in dependent smokers; Perkins et al., 2017). Presence or absence of nicotine dependence was confirmed by DSM-V criteria (APA, 2013), which dependent smokers currently met and non-dependent smokers could never have met (i.e., no history of dependence). To further compare these subgroups on dependence, all also completed the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton et al., 1991), as well as the MNWS withdrawal scale (Hughes and Hatsukami 1986) upon arrival to the first session following overnight abstinence. As expected, dependent and non-dependent participants differed significantly on mean (SD) smoking history characteristics, respectively, of 14.8 (3.7) vs 1.4 (0.7) cigarettes per day, $t(26) = 9.54$, $p < 0.001$, and 4.2 (1.8) vs 0.1 (0.4) FTND score, $t(26) = 5.73$, $p < 0.001$, as well as on MNWS score after overnight abstinence of 40.7 (18.8) vs 19.0 (9.0), $t(26) = 2.91$, $p < 0.01$. Also as expected, they did not differ significantly on age, 32.1 (11.2) vs. 24.3 (7.0) years old, respectively, $t(26) = 1.72$, $p < 0.10$, and their self-identified ethnic representation was similar, with 90% vs 71% Caucasian, and the other 2 from each group comprising more than one race and either African American or Asian.

2.2. Research cigarettes

Spectrum investigational research cigarettes, manufactured by 22nd Century Group (Clarence NY; http://www.xxiicentury.com/), were obtained from NIDA's Drug Supply Program (see Perkins et al., 2016a). Selected for the current study were all those cigarettes that differed in nicotine contents but were similar on "tar" yield (so differing only in nicotine per se). Nicotine contents of these cigarettes were 17, 11, 5, 2, 1, and 0.4 mg (averaging two Spectrum batches sent by NIDA), and all had about 9–10 mg "tar". Not available is a true "placebo" Spectrum, with zero nicotine content. (Comparing their "yields" by FTC method with commercial brands, which is more familiar and estimates the inhaled portion of nicotine rather than total contents in the cigarette, these Spectrum research cigarettes correspond to approximately 0.8, 0.6, 0.26, 0.12, 0.07, and 0.03 mg nicotine; see http://grants.nih.gov/grants/guide/notice-files/NOT-DA-14-004.html. Most commercial brands yield about 0.9 mg nicotine of inhaled nicotine, with roughly 10 mg "tar"; USDHHS, 2010) As described below in Procedures, all discrimination testing sessions involved comparing the very lowest content cigarette, 0.4 mg/g, with each of the higher nicotine content cigarettes. Just one of these "higher" nicotine cigarettes was compared with the 0.4 mg/g cigarette in a given session. To clearly differentiate this comparison cigarette with the others tested, this lowest is often called the "ultra-low" nicotine cigarette.

2.3. Smoke exposure control

Intake from all cigarettes during all sessions (see 2.4 Procedures, below) was fixed at 4 puffs per trial, just as in our prior discrimination testing via smoking (Perkins et al., 2016a, 2016b) as well as in the only prior controlled human test of discriminating any drug inhaled by smoking, on marijuana (Chait et al., 1988). All smoking in this study was done using the portable Clinical Research Support System (CReSS; Borgwaldt KC, Inc., Richmond VA), according to procedures common to our past research (e.g., Perkins et al., 2016a), with one puff every 30 s and a new cigarette on each trial. Timing of each puff was determined by computer-displayed instructions, so that a 2-s puff duration standardized smoke intake at approximately 60 ml per puff, which is similar to most ad lib puffing (Blank et al., 2009; Perkins et al., 2012). The CReSS assesses puff number, total puff volume (total intake across all puffs from a single cigarette), and average volume per puff, saving these data electronically and allowing puff topography to be compared with our 60 ml per puff target. This pattern of smoke exposure allowed intervals of 15 min between trials while minimizing smoking satiation or toxicity. Smoking 4 puffs is also typical exposure at the point a smoker forms expectations about a cigarette, which clearly impact the subsequent reinforcing and other effects of that cigarette (Gu et al., 2015; Hasenfratz et al., 1993; see also Perkins et al., 2001; Perkins et al., 1994, 1996).

2.4. Procedures

2.4.1. General

All study sessions involved testing ability to discriminate between the ultra-low (0.4 mg/g) nicotine content cigarette versus one of the higher nicotine content Spectrum cigarettes (≥1 mg/g). Thus, Spectrum cigarettes with previously described nicotine contents of 17, 11, 5, 2, and 1 mg/g were separately tested, one per session, on discriminability from the 0.4 mg/g cigarette. Behavioral discrimination was determined by reliable detection of which cigarette was which across the separate exposures to each under blind conditions during the session (e.g., Bolin et al., 2016; Perkins, 2011; see 2.4.2. Specific session procedures). Each participant's total number of sessions depended on success of discrimination behavior, as participation ended when the lowest nicotine content cigarette he or she could reliably discriminate from the ultra-low (0.4 mg/g) was determined, identifying the "threshold" dose. The next lowest content cigarette below their threshold cigarette, which by definition they failed to discriminate, was labeled their "subthreshold" dose. These procedures were developed and evaluated (Perkins et al., 2016a) prior to studies of nicotine discrimination thresholds in dependent smokers via Spectrum cigarettes (Perkins