Title: Cue-Induced Drug Seeking and Its Association with Craving and Dependence in Cigarette Smokers

Running title: Drug-Seeking in cigarette smokers

Solinas Marcello, PhD [1,2], Chauvet Claudia MD, PhD [2], Lafay-Chebassier Claire PhD [1,3,4], Vanderkam Paul, MD, PhD [1], Barillot Lila, M.S. [2,5], Moeller Scott J, PhD [6], Goldstein Rita Z, PhD [7], Noël Xavier, PhD [8], Jaafari Nematollah, MD, PhD [2,4, 9], Chatard Armand, PhD [2,5]

[1]Laboratoire de Neurosciences Expérimentales et Cliniques, Université de Poitiers, INSERM, U-1084, Poitiers, France.
[2]Unité de Recherche Clinique Pierre Deniker, Centre Hospitalier Henri Laborit, Poitiers, France
[3]INSERM, Centre d'Investigation Clinique CIC 1402, Université de Poitiers, CHU Poitiers, Poitiers, France
[4]Service de Pharmacologie Clinique, CHU Poitiers, Poitiers, France
[5]Université de Poitiers, Université de Tours, CNRS 7295, CeRCA, Poitiers, France. France.
[6]Department of Psychiatry and Behavioral Health, Renaissance School of Medicine at Stony Brook University, Stony Brook, NY 11794, USA
[7] Psychiatry & Neuroscience, Icahn School of Medicine at Mount Sinai, NY, USA
[8] Université Libres de Bruxelles, Belgium
[9]Service Hospitalo-Universitaire de Psychiatrie et de Psychologie Médicale, Centre Hospitalier Henri Laborit, Poitiers, France

Corresponding Author :
Dr Marcello Solinas
Université de Poitiers, INSERM U-1084
Laboratoire des Neurosciences Expérimentales et Cliniques
1, rue Georges Bonnet, TSA 51106
86073 Poitiers Cedex 9, France
Tel : 00 33 549366343
E-mail: marcello.solinas@univ-poitiers.fr

Abstract

Increased salience of drug-related cues over non-drug reinforcers can drive drug use behaviors and contribute to tobacco use disorder (TUD). An important scientific and clinical goal is to effectively measure this elevated drug-seeking behavior in TUD. However, most TUD assessments rely on self-reported cravings and cigarette consumption, not providing an objective measure of cue-induced drug seeking. The probabilistic image choice (PIC) task, initially developed and validated for cocaine use disorder (and since validated in users of methamphetamine and opioids), investigates the choice of viewing drug-related pictures as compared to other salient pictures (e.g., pleasant and unpleasant cues). This study aimed to develop and validate the PIC task for TUD and evaluate the associations between behavioral choice and tobacco craving, daily cigarette consumption, and nicotine dependence (the Fagerström score). We recruited 468 smokers and 121 nonsmokers using the Prolific online platform. Participants performed the PIC task twice (at a one-month interval) and completed other measures relevant to TUD. As expected, compared to nonsmokers, tobacco smokers selected to view significantly more tobacco images and less pleasant (non-drug reinforcer) images, a profile that remained stable at retest. Drug seeking on the PIC task was associated with craving but not with the other tobacco dependence measures, suggesting that the task is better at modeling current drug "wanting" rather than cumulative nicotine exposure or physical dependence. In conclusion, these results suggest that the PIC task can be a valuable tool for objectively assessing craving-associated tobacco seeking in TUD.

Implications section, which should provide a brief description about what the study adds (50-100 words).

Current measures of tobacco use disorder (TUD) rely on self-reports of consumption, dependence and craving and do not take into consideration the role of drug-related cues in driving tobacco seeking. This study shows that the probabilistic image choice (PIC) task provides an objective, reliable proxy measure of drug-seeking behavior in cigarette smokers that is linked to craving and desire for smoking but not to other measures of TUD. Therefore, the PIC task may be a useful complementary tool for the classification, diagnosis, and prognosis of TUD.

Introduction

Tobacco use disorder (TUD) is the major preventable cause of morbidity and mortality in the world [1]. In the last decades, prevention campaigns have been effective in educating the general population about the risks associated with tobacco smoking, contributing to reduced prevalence of TUD [2,3]. However, with the increase in global population, the total number of smokers has increased and TUD is estimated to cause 7 million excess deaths per year [2,3]. Investigating the factors that drive tobacco use can provide a deeper understanding of the mechanisms underlying TUD and help health-care providers to improve treatment and prevention efforts for this behavioral disorder.

A critical aspect of TUD is relapse, occurring within a year of a quit attempt in more than 50% of abstinent smokers [4]. Drug-related cues play a major role in relapse and the maintenance of drug addiction [5–10]. Indeed, drugs activate dopamine circuits and produce strong associations between the drugs' reinforcing effects and environmental cues associated with drug use [11,12]. This process underlies the attribution of excessive value to these cues that become irresistible "motivational magnets" driving drug seeking behavior [13] even when awareness of such choice is compromised [14–16]. Moreover, because drugs activate the dopamine system more intensely than natural rewards, over time the value of drugs and related cues increases at the expense of alternative reinforcers [17]. Such drug-biased incentive motivation is also important for TUD because, although nicotine is a relative weak reinforcer in animal models of addiction, it increases the incentive properties of drug-associated cues so that they can act as reinforcers even in the absence of nicotine [18]. Nevertheless, aside from tobacco self-administration paradigms [19], impractical and/or unethical in many settings, current measures of TUD such as the Fagerström Test for Nicotine Dependence (FTND) rely mostly on self-reported measures of craving and dependence and do not provide an objective measure of cue-induced drug seeking. Here, we instead used a task that provides an operant measure of drug-seeking behavior, which can be a useful tool for ascertaining disease severity [20], consistent with the call to use objectively-measured outcome variables in clinical trials in drug addiction [21].

The probabilistic image choice (PIC) task was designed as a tool to objectively model drug-related choice behavior in individuals with cocaine use disorder (both active and abstinent users) who had a higher choice preference for viewing cocaine pictures than healthy control subjects [22]. Notably, although associated with less awareness of such drug-biased choice [23], the selection of cocaine over pleasant images (the alternative reinforcer) was predictive of both current and future drug use [24]. The PIC task has been successfully adapted

to methamphetamine [25] and opiate [26] use disorders but its potential use for investigating TUD has not been explored.

In this study, we adapted the PIC task to tobacco smoking and investigated differences between 468 smokers and 121 non-smokers, as well as test-retest stability of drug-seeking behavior after a one-month interval. We further investigated whether drug-seeking behavior on the PIC task correlated with other measures of TUD such as craving, cigarette consumption, quit attempts and motivation to quit, and severity of dependence. We hypothesized that smokers would choose more tobacco-related images, and less pleasant images (indicative of a drug>pleasant shift in valuation and behavior), than non-smokers. Additionally, we hypothesized that a preference for tobacco images would be associated with self-reported measures of craving, daily cigarette consumption, quit attempt/motivation to quit, and severity of tobacco dependence.

Methods

Participants

Participants were 468 regular smokers (i.e., individuals who smoked at least 5 cigarettes per day over the last year) and 121 nonsmokers (i.e., never smokers) recruited via the research online platform Prolific (https://www.prolific.co/, see Table 1 for sample demographics). Participants were eligible for the study if they were residents from the UK or the USA, and if they were native English speakers. In an effort to oversample individuals who smoked cigarettes for several years, only participants older than 35 were recruited. Smokers completed the study on March 3rd 2022 (Time 1). About 30 days later, on April 4th 2022, the participants were recontacted via the platform Prolific and invited to respond to a follow-up survey (Time 2). A total of 286 participants completed the second wave of data collection (182 participants could not be reached, were not available, or did not respond to the survey). Of these, 13 participants were excluded because they reported smoking less than 5 cigarettes. Nonsmokers completed the study on February 2nd, 2023. All participants were debriefed and received 10£/hour as compensation.

The study was approved by the local institutional ethical committee (Comité d'Ethique de la Recherche des Universités de Tours et Poitiers) and conforms with the European regulations on data protection.

Table 1.
Demographic characteristics

Smoking Status	**Age** ± SD (Min-Max)	Gender	Frequency	Percent	Valid Percent
Smokers	47.47 ± 9.50 (35-75)	Female	206	44.02	49.16
		Male	211	45.08	50.36
		Nonbinary	2	0.43	0.48
		Missing	49	10.47	
		Total	468	100.00	
Nonsmokers	50.58 ± 10.46 (34-76)	Female	60	49.59	50.42
		Male	59	48.76	49.58
		Nonbinary	0	0.00	0.00
		Missing	2	1.65	
		Total	121	100.00	

Procedure

Participants were initially classified as smokers or nonsmokers based on information in the Prolific database. After a few demographic questions (gender, age, nationality, etc.), smokers provided information about their tobacco consumption (the number of cigarettes smoked per day), quit attempts and motivation to quit followed by a self-reported questionnaire on craving [27]. Then all participants completed the PIC task. Finally, smokers were asked to complete the Fagerström test for nicotine dependence [28]. These measures are described in detail below.

Probabilistic Image Choice (PIC) Task

The 'probabilistic' version of the original choice task developed by Moeller et al. (2009) was adapted and used in the present study to measure the behavioral tendency to choose drug as compared to other salient (pleasant and unpleasant) and neutral pictures. Participants were presented with four decks of flipped-over cards. Participants were informed that each deck contains neutral, pleasant, unpleasant, and drug-related pictures, but that some decks contain more pictures of one type than the others. Participants were asked to find and select the deck(s) that they found most appealing. Upon selection, the picture was uncovered to fit the entire screen and passively viewed for 2000ms (Fig. S1). Participants could then select again from the same deck or switch to another one. Each deck contained a total of 30 pictures, which unbeknownst to the participants were pseudorandomly sorted according to the following two constraints: (A) there were no picture repetitions between the four decks; and (B) each deck contained 26 pictures (87%) of one picture category (e.g., tobacco), two pictures (7%) of another category (e.g., pleasant), and one picture (3%) of each of the remaining two categories (e.g., unpleasant, neutral). These percentages were selected to reduce awareness of deck identity, while still allowing for preference to be established. A run terminated when participants selected from a particular deck for a total of eight times. Participants completed four runs. To further reduce awareness of deck identity, and to overcome the potential impact on results of perseverative responding (e.g., repeatedly choosing from the same deck across the runs), the dominant picture categories were pseudorandomized across the decks between the runs (i.e., the deck location of the four picture categories did not repeat across the runs). The total number of cards selected per picture category (neutral, pleasant, unpleasant, and tobacco-related) across the four runs was summed. As in previous studies [22,24], drug seeking was operationalized as the preference for viewing tobacco over pleasant images.

We replaced the pictures used in the Moeller publications for improved picture quality and to fit online administration to people residing across two continents. The current version of the task, adapted for TUD, included 30 pleasant, 30 neutral, and 30 unpleasant pictures selected from the International Affective Picture System (Lang et al., 1998), depicting pleasant scenes (e.g., smiling faces, baby images, natural landscapes), neutral scenes (e.g., places, household objects), or unpleasant scenes (e.g., sad faces, violent images), respectively. The fourth picture category comprised of 30 images related to smoking cigarettes, tobacco, and tobacco use (e.g., cigarette packs, cigarette smoke, people smoking) derived from the Geneva Smoking Pictures library [29]. The current version of the task was initially developed in Python and later converted to JavaScript to enable online functionality. The task is freely accessible via the Open Science Framework link: https://osf.io/n23rx/..

Cigarettes consumption

Smokers were requested to report the quantity of cigarettes they typically smoke daily at both study sessions. Because this measure was heavily skewed to the right, it was transformed into a 4-point response scale, mirroring the one utilized in the Fagerström test (≤10 cigarettes per day = 0, 11 to 20 cigarettes per day = 1, 21 to 30 cigarettes per day = 2, and ≥31 cigarettes per day = 3). At Time 1, participants also indicated whether they have already tried to quit smoking in the past and to estimate the number of times they attempted to quit smoking. Finally, participants reported their motivation to quit smoking in the next 6 months on a 10-point Likert scale ranging from 1 = very weak to 10 = very strong.

Craving questionnaire

The brief questionnaire of smoking urges (QSU-brief; [27]) was used at both sessions to measure craving for cigarettes. This 10-item instrument assesses the desire to consume cigarettes in the immediate present (representative items: “All I want right now is a cigarette” and “I have an urge for a cigarette”). Participants indicated their response to each item using a 7-point Likert scale (1 = strongly disagree and 7 = strongly agree). In the present sample, the internal validity of the scale was satisfactory (Cronbach’s alpha = .95 and .96, at Time 1 and Time 2, respectively). The responses to the 10 items were summed to form a composite score of craving.

Nicotine dependence

At Time 1, participants also completed the Fagerström Test for Nicotine Dependence [28]. This is a standard instrument for assessing the severity of addiction to nicotine, providing an ordinal measure of nicotine dependence related to cigarette smoking. It contains six items that

evaluate the quantity of cigarette consumption, the compulsion to use, and dependence (e.g., "Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in the cinema?"). The six items were summed to yield a total score of 0-10.

Statistical analyses

At Time 1, we conducted a mixed 2 (Smoking status: smoker versus nonsmoker) x 4 (picture type: tobacco-related, pleasant, unpleasant, and neutral) analysis of variance (ANOVA) with repeated measures on the latter factor to examine whether TUD is associated with a higher preference for tobacco-related stimuli in the adapted PIC task. We followed up significant interactions with post-hoc t-tests. Intraclass correlation (ICC) coefficients were also calculated to assess the stability of drug seeking behavior and craving after a 1-month follow-up. Furthermore, we conducted Person's correlations between the normalized and a priori designated metric indexing preference for viewing tobacco images over pleasant images (i.e., number of selections of tobacco images minus pleasant images) with all TUD-related measures (encompassing severity of cigarette consumption, craving, quit attempts and motivation to quit, and the Fagerström score). All data analyses were performed with R version 3.6.1 (R Core Team, 2021). Data and statistical analyses are freely accessible via the Open Science Framework link: https://osf.io/n23rx/.

Results

Table 2 summarizes the main tobacco-related information in the population of smokers involved in our study.

Table 2.
Descriptive Statistics of TUD-related measures

	Number of Cigarettes T1	**Number of Cigarettes T2**	**Number of Quit Attempts T1**	**Number of Quit Attempts T2**	**Quit Motivation T1**	**Fagerström T1**	**Craving T1**	**Craving T2**
Valid N	453	271	430	250	415	468	468	286
Mean	15.17	15.35	3.02	3.19	5.19	4.39	37.71	36.87
SD	7.64	7.57	3.21	2.98	2.81	1.95	15.27	16.79
Minimum	5.00	5.00	0.00	0.00	0.00	0.00	10.07	10.03
Maximum	50.00	50.00	25.00	15.00	10.00	10.00	69.92	69.85

At time 1 (baseline), the 2 (smoking status) x 4 (picture type) mixed ANOVA showed no main effect of smoking status ($F(1, 586) = 0.014$, $p = 0.90$, $\eta^2_p = 0.001$). However, there was a significant main effect of picture type ($F(3, 1758) = 170.31$, $p < 0.0001$, $\eta^2_p = 0.225$), indicating that participants generally chose more pleasant images than other types (all pair-wise comparison tests, *p*s < .001). Of greater interest, this main effect was qualified as expected by a significant interaction ($F(3, 1758) = 8.10$, $p < 0.001$, $\eta^2_p = 0.014$) (Fig. 1). Post-hoc tests revealed that while there were no significant differences between smokers and non-smokers in the selection of neutral ($p = .144$) or unpleasant images ($p = .560$), tobacco smokers selected significantly more tobacco-related images ($p < .001$) and significantly fewer pleasant images ($p = .036$) than non-smokers.

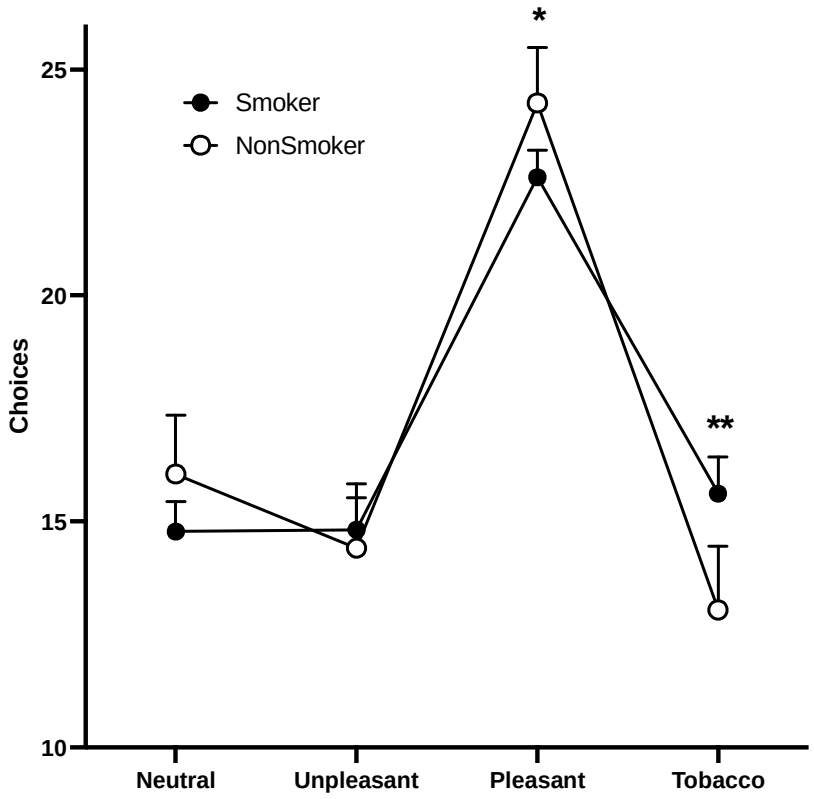

Fig. 1. Performance in the PIC task in smokers and nonsmokers. A) Number of selection of images in each category in the PIC task for smokers (full circles, N = 468) and nonsmokers (empty circles, N = 121). Data are represented as mean ± 95% CI. * and **, $p < 0.05$ and $p < 0.001$ smokers vs. nonsmokers, respectively.

Within the smokers, the preference for viewing tobacco compared to other positively valenced images (number of selections of tobacco images minus pleasant images) was correlated across both Time 1 and Time 2 (ICC = .70, $p < .0001$), indicating that the probabilistic choice test has a good level of test-rested reliability (Fig. 2). There were also high intercorrelations between T1 and T2 for craving scores (r (286) = .72, $p < .001$); number of cigarettes (r (286) = .88, $p < .001$) and quit attempts (r (286) = .81, $p < .001$).

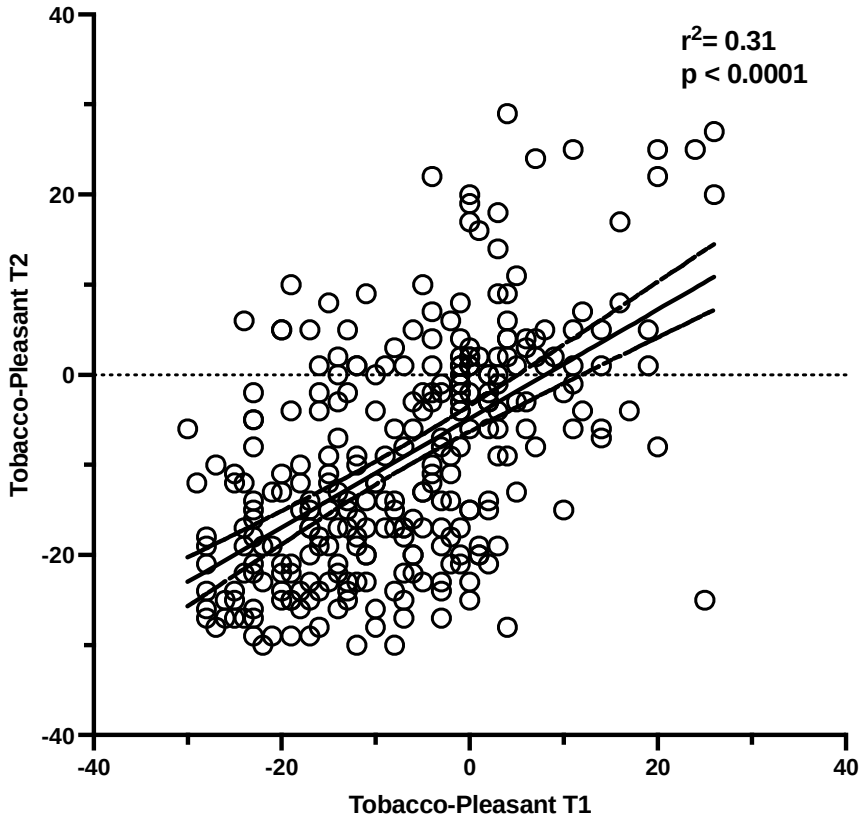

Fig. 2. Test-retest reliability of tobacco choice on the PIC task. Correlation between the direct contrast of the selection of tobacco vs. pleasant images on the PIC task at Time 1 and Time 2, separated by a one-month interval, in smokers (N = 286). Dotted lines show 95% CI.

Among the smokers, we also investigated Pearson correlations between our selected dependent measure (tobacco vs. pleasant viewing choice) with the tobacco-related variables (table 3). Drug>pleasant choices were positively correlated with craving both at time 1 (r (468) = .215, p < .001) and at time 2 (r (286) = .348, p < .001) (the higher the self-reported craving, the higher the drug>pleasant choice) (Fig. S2). In addition, drug>pleasant choices at time 1 prospectively predicted craving at time 2 (r (286) = .286, p < .001). Drug>pleasant choice was uncorrelated with the other TUD-related measures, at either T1 (r<0.098) or T2 (r<0.126). For correlations within the other drug use measures see Table 3.

tions (and p-values) of TUD-related measures

T1–bacco-asant erence	T1–Numbers of Cigarettes	T1–Quit Attempts	T1–Quit Motivation	T1–Fagerström	T1–Craving	T2–Tobacco-Pleasant Preference	T2–Number Cigarett
13	—						
60	0.017	—					
98^{+}	**−0.104***	**0.356*****	—				
39	**0.668*****	0.027	**−0.105***	—			
14***	**0.145****	**0.111***	**0.139****	**0.283*****	—		
48***	0.048	−0.068	−0.126^{+}	0.047	**0.224*****	—	
73	**0.880*****	−0.042	**−0.140***	**0.661*****	**0.138***	0.053	—
54	−0.032	**0.813*****	**0.289*****	0.048	**0.161****	−0.052	−0.075
86***	0.117^{+}	**0.151***	0.083	**0.264*****	**0.717*****	**0.348*****	**0.169****

Fageström test were assessed only at T1.

Discussion

In this study, we adapted the PIC task [22] for measuring tobacco-seeking behavior (choice of viewing tobacco-related as compared to other salient and neutral images) in a relatively large sample of cigarette smokers. We found that the choice to view tobacco images was higher, and the choice to view pleasant images was lower, in smokers than nonsmokers. The preference for viewing tobacco-related images over pleasant images correlated with self-reported levels of craving both cross-sectionally and longitudinally but not with other measures of TUD (including number of cigarettes smoked, quit attempts and motivation, and scores on the Fagerström questionnaire).The tobacco over pleasant image choice was stable when tested one month apart in the smokers (tested with an ICC and a correlation with craving). Collectively, these results suggest that the PIC task provides a relatively stable indicator of drug-seeking behavior that is linked to current incentive motivation for tobacco, rather than other TUD severity measures or cumulative nicotine exposure. Therefore, this task could serve as a valuable complementary tool for investigating drug "wanting" and seeking behavior in the context of TUD.

Our results showing elevated drug>pleasant choice on this tobacco-adapted PIC task are consistent with prior versions of the task that were developed for use in cocaine use disorder [22] and validated for methamphetamine and opioid use disorders [25,26]. A common finding across these studies was that compared to healthy controls, people with drug use disorders show increased choice for viewing the drug images, and decreased choice of viewing the pleasant images [22,25]. Interestingly, though, choice was not correlated with other parameters or severity of TUD such as the number of cigarettes smoked, the number of quit attempts (an indication of problematic use), motivation to quit, or the Fagerström score, the most common test of tobacco dependence. This pattern suggests that drug biased choice is primarily related to craving (current desire for drug), rather than overall dependence or duration/severity of use. It would be interesting to evaluate such choice behavior as a clinically relevant outcome variable in future clinical research settings and trials.

This pattern of results demonstrating a drug-relevant choice bias at the expense of alternative reinforcers is consistent with the Impaired Response Inhibition and Salience Attribution (I-RISA) model of addiction [30]. Based on clinical and brain-imaging data in humans as well as data from animal studies, this model postulates enhanced salience attribution to the drug and drug related cues at the expense of alternative reinforcers and with a concomitant decrease in inhibitory control in people with addiction, as attributed to dysfunction in higher-order cortical brain regions, including the prefrontal cortex, underlying salience/value attribution,

cognitive control, and interoception [30–33]. These results are also in line with other influential theories in drug addiction including incentive motivation [34], aberrant learning of drug-related stimuli [11,12] and drug-induced allostasis [35], which are based on a rich animal literature. Our current results using behavioral drug-seeking, analogous to non-human self-administration models of addiction [36], allow a translational bridge that is not dependent on intact processes of self-awareness, interoception, or insight (needed for accurate self-reports) [37].

Important features of procedures to measure craving are their validity and their reliability [38]. Validity refers to the fact that the experimental measure is related to the phenomenon that it is meant to assess. In this context, the fact that choices of tobacco images in the PIC task were consistently correlated to self-reported craving suggest that they depend at least in part on the same underlying biological process. Given the strong evidence for the role of cues and craving in addiction and in relapse [33,39–42], which has been confirmed by recent metanalyses [6,10,43], the PIC task is likely to provide a valid measure of addiction-related processes. On the other hand, reliability refers to the ability of the test to provide scores that are consistent and stable [38]. The fact that choices of tobacco images in the PIC task at two different time points were highly correlated demonstrates a good test-retest reliability. Thus, the PIC appears to be both a valid and reliable measure of processes involved in drug seeking which could be used in longitudinal studies.

An important consideration and possible limitation of this study is that it was performed online, in a non-controlled environment. Participants with TUD were not formally diagnosed by a clinical rater, included based on self-reported cigarette use. There is also potential for distraction and reduced engagement compared with a laboratory setting, although we note that this would likely have introduced noise that would have diluted our effects rather than enhanced them. Second, the current study was conducted in a community population of current smokers not seeking to quit tobacco use, and thus the results may not generalize to treatment-seekers. Another technical consideration stemming from this online sampling is that we could not standardize smoking abstinence at the time of the test. Participants could have smoked immediately before (possibly during) or several hours before taking the tests, precluding our ability to account for the pharmacological effects of nicotine or withdrawal, shown to influence craving [44,45]. Variability in drug choice and craving are expected based on our results in people with cocaine addiction, such that both are enhanced with more recent use [23]. Another possible limitation is that we selected participants who were 35 years or older and younger populations remain to be studied. In addition, smokers and non-smokers were

tested at different times and the impact of the pictures included remains to be studied in larger and simultaneously studied cohorts.

The primary finding of this study is that the PIC task provides an objective, reliable proxy measure of drug-seeking behavior in cigarette smokers that is linked to craving and desire for smoking. This behavioral tool for assessing drug-seeking could be useful in the classification, diagnosis, and prognosis of TUD. Future work can determine whether the PIC task can serve as a useful predictor of future outcomes (e.g., abstinence) in treatment-seeking people with TUD.

Funding statement
This work was supported by the Centre National pour la Recherche Scientifique, the Institut National de la Santé et de la Recherche Médicale, the University of Poitiers, the IRESP and the Aviesan Alliance (IRESP-19-ADDICTIONS-20, to MS), the National Institute on Drug Abuse (NIDA) (R01DA051420, R01DA049733, and R21DA051179, to SJM and R01DA047851, R01AT010627, R01DA048301, R01DA049547, R21DA054281, and 271201800035C-0-0-1 RZG).

Declarations of competing interest: The authors declare no competing interests.

Author contributions:
Conceptualization (MS, CC, NJ, AC), Data curation (AC), Formal Analysis (MS, AC), Funding Acquisition (MS, NJ, AC), Investigation (AC), Methodology, (MS, CC, CLC, PV, LB, SJM, RZG, XN, NJ, AC), Project Administration (MS, AC), Resources (MS, CC, CLC, PV, LB, SJM, RZG, XN, NJ, AC), Software (SJM, AC), Writing-original draft (MS, AC), Writing- review and editing (MS, CC, CLC, PV, LB, SJM, RZG, XN, NJ, AC).

References

1. World Health Organization. *WHO Global Report on Trends in Prevalence of Tobacco Smoking 2000-2025*. 2nd ed. World Health Organization; 2018. Accessed November 20, 2022. https://apps.who.int/iris/handle/10665/272694
2. Dai X, Gakidou E, Lopez AD. Evolution of the global smoking epidemic over the past half century: strengthening the evidence base for policy action. *Tob Control*. 2022;31(2):129-137. doi:10.1136/tobaccocontrol-2021-056535
3. Reitsma MB, Kendrick PJ, Ababneh E, et al. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. *The Lancet*. 2021;397(10292):2337-2360. doi:10.1016/S0140-6736(21)01169-7
4. García-Rodríguez O, Secades-Villa R, Flórez-Salamanca L, Okuda M, Liu SM, Blanco C. Probability and predictors of relapse to smoking: Results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug and Alcohol Dependence*. 2013;132(3):479-485. doi:10.1016/j.drugalcdep.2013.03.008
5. Adinoff B. Neurobiologic Processes in Drug Reward and Addiction. *Harvard Review of Psychiatry*. 2004;12(6):305-320. doi:10.1080/10673220490910844
6. Betts JM, Dowd AN, Forney M, Hetelekides E, Tiffany ST. A Meta-Analysis of Cue Reactivity in Tobacco Cigarette Smokers. *Nicotine Tob Res*. 2021;23(2):249-258. doi:10.1093/ntr/ntaa147
7. Field M, Cox W. Attentional bias in addictive behaviors: A review of its development, causes, and consequences. *Drug and Alcohol Dependence*. 2008;97(1-2):1-20. doi:10.1016/j.drugalcdep.2008.03.030
8. Franken IHA. Drug craving and addiction: integrating psychological and neuropsychopharmacological approaches. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2003;27(4):563-579. doi:10.1016/S0278-5846(03)00081-2
9. Perry CJ, Zbukvic I, Kim JH, Lawrence AJ. Role of cues and contexts on drug-seeking behaviour: Cues, contexts and drug seeking. *Br J Pharmacol*. 2014;171(20):4636-4672. doi:10.1111/bph.12735
10. Vafaie N, Kober H. Association of Drug Cues and Craving With Drug Use and Relapse: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2022;79(7):641. doi:10.1001/jamapsychiatry.2022.1240
11. Di Chiara G. Drug addiction as dopamine-dependent associative learning disorder. *Eur J Pharmacol*. 1999;375(1-3):13-30. doi:10.1016/s0014-2999(99)00372-6
12. Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu Rev Neurosci*. 2006;29:565-598. doi:10.1146/annurev.neuro.29.051605.113009
13. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev*. 1993;18(3):247-291. doi:10.1016/0165-0173(93)90013-p
14. Goldstein RZ, Craig AD (Bud), Bechara A, et al. The Neurocircuitry of Impaired Insight in Drug Addiction. *Trends in Cognitive Sciences*. 2009;13(9):372-380. doi:10.1016/j.tics.2009.06.004
15. Maracic CE, Moeller SJ. Neural and Behavioral Correlates of Impaired Insight and Self-awareness in Substance Use Disorder. *Curr Behav Neurosci Rep*. 2021;8(4):113-123. doi:10.1007/s40473-021-00240-x
16. Moeller SJ, Goldstein RZ. Impaired self-awareness in human addiction: deficient attribution of personal relevance. *Trends in Cognitive Sciences*. 2014;18(12):635-641. doi:10.1016/j.tics.2014.09.003
17. Wise RA, Koob GF. The Development and Maintenance of Drug Addiction. *Neuropsychopharmacol*. 2014;39(2):254-262. doi:10.1038/npp.2013.261
18. Caggiula AR, Donny EC, White AR, et al. Cue dependency of nicotine self-administration and smoking. *Pharmacology Biochemistry and Behavior*. 2001;70(4):515-530. doi:10.1016/S0091-3057(01)00676-1
19. Lerman C, LeSage MG, Perkins KA, et al. Translational research in medication development for nicotine dependence. *Nat Rev Drug Discov*. 2007;6(9):746-762. doi:10.1038/nrd2361

20. Parikh A, Moeller SJ, Garland EL. Simulated opioid choice linked to opioid use disorder severity among veterans with chronic pain: initial validation of a novel paradigm. *Am J Drug Alcohol Abuse*. 2022;48(4):403-412. doi:10.1080/00952990.2021.2007258
21. Goldstein RZ. Outcomes in Clinical Trials for Addiction. Published online 2022.
22. Moeller SJ, Maloney T, Parvaz MA, et al. Enhanced Choice for Viewing Cocaine Pictures in Cocaine Addiction. *Biological Psychiatry*. 2009;66(2):169-176. doi:10.1016/j.biopsych.2009.02.015
23. Moeller SJ, Maloney T, Parvaz MA, et al. Impaired insight in cocaine addiction: laboratory evidence and effects on cocaine-seeking behaviour. *Brain*. 2010;133(5):1484-1493. doi:10.1093/brain/awq066
24. Moeller SJ, Beebe-Wang N, Woicik PA, Konova AB, Maloney T, Goldstein RZ. Choice to view cocaine images predicts concurrent and prospective drug use in cocaine addiction. *Drug and Alcohol Dependence*. 2013;130(1-3):178-185. doi:10.1016/j.drugalcdep.2012.11.001
25. Moeller SJ, Okita K, Robertson CL, et al. Low Striatal Dopamine D2-type Receptor Availability is Linked to Simulated Drug Choice in Methamphetamine Users. *Neuropsychopharmacol*. 2018;43(4):751-760. doi:10.1038/npp.2017.138
26. Moeller SJ, Hanley AW, Garland EL. Behavioral preference for viewing drug *v*. pleasant images predicts current and future opioid misuse among chronic pain patients. *Psychol Med*. 2020;50(4):644-652. doi:10.1017/S0033291719000461
27. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res*. 2001;3(1):7-16. doi:10.1080/14622200020032051
28. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict*. 1991;86(9):1119-1127. doi:10.1111/j.1360-0443.1991.tb01879.x
29. Khazaal Y, Zullino D, Billieux J. The Geneva Smoking Pictures: development and preliminary validation. *Eur Addict Res*. 2012;18(3):103-109. doi:10.1159/000335083
30. Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry*. 2002;159(10):1642-1652. doi:10.1176/appi.ajp.159.10.1642
31. Goldstein RZ, Craig AD (Bud), Bechara A, et al. The Neurocircuitry of Impaired Insight in Drug Addiction. *Trends in Cognitive Sciences*. 2009;13(9):372-380. doi:10.1016/j.tics.2009.06.004
32. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*. 2016;3(8):760-773. doi:10.1016/S2215-0366(16)00104-8
33. Zilverstand A, Huang AS, Alia-Klein N, Goldstein RZ. Neuroimaging Impaired Response Inhibition and Salience Attribution in Human Drug Addiction: A Systematic Review. *Neuron*. 2018;98(5):886-903. doi:10.1016/j.neuron.2018.03.048
34. Berridge KC, Robinson TE. Liking, wanting, and the incentive-sensitization theory of addiction. *American Psychologist*. 2016;71(8):670-679. doi:10.1037/amp0000059
35. Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*. 2001;24(2):97-129. doi:10.1016/S0893-133X(00)00195-0
36. Moeller SJ, Stoops WW. Cocaine choice procedures in animals, humans, and treatment-seekers: Can we bridge the divide? *Pharmacology Biochemistry and Behavior*. 2015;138:133-141. doi:10.1016/j.pbb.2015.09.020
37. Moeller SJ, Hajcak G, Parvaz MA, Dunning JP, Volkow ND, Goldstein RZ. Psychophysiological prediction of choice: relevance to insight and drug addiction. *Brain*. 2012;135(11):3481-3494. doi:10.1093/brain/aws252
38. Sayette MA, Shiffman S, Tiffany ST, Niaura RS, Martin S, Shadel WG. The measurement of drug craving. Published online 2009:26.
39. Sinha R. The clinical neurobiology of drug craving. *Current Opinion in Neurobiology*. 2013;23(4):649-654. doi:10.1016/j.conb.2013.05.001
40. Skinner MD, Aubin HJ. Craving's place in addiction theory: Contributions of the major models. *Neuroscience & Biobehavioral Reviews*. 2010;34(4):606-623. doi:10.1016/j.neubiorev.2009.11.024
41. Tiffany ST. Cognitive Concepts of Craving. 1999;23(3):10.

42. Wray JM, Gass JC, Tiffany ST. A Systematic Review of the Relationships Between Craving and Smoking Cessation. *Nicotine & Tobacco Research*. 2013;15(7):1167-1182. doi:10.1093/ntr/nts268
43. Gass JC, Motschman CA, Tiffany ST. The relationship between craving and tobacco use behavior in laboratory studies: A meta-analysis. *Psychology of Addictive Behaviors*. 2014;28(4):1162-1176. doi:10.1037/a0036879
44. Perkins KA, Briski J, Fonte C, Scott J, Lerman C. Severity of tobacco abstinence symptoms varies by time of day. *Nicotine & Tobacco Research*. 2009;11(1):84-91. doi:10.1093/ntr/ntn003
45. Schlam TR, Piper ME, Cook JW, Fiore MC, Baker TB. Life 1 Year After a Quit Attempt: Real-Time Reports of Quitters and Continuing Smokers. *ann behav med*. 2012;44(3):309-319. doi:10.1007/s12160-012-9399-9