STUDY PROTOCOL

The effect of acute abstinence in smokers on cognitive performance and craving

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Background

Nicotine withdrawal symptoms are one of the main obstacles to successful cessation (Tiffany, 1990; West & Schneider, 1987). A better understanding of the mechanisms underlying withdrawal is therefore crucial in order to guide the development of smoking cessation treatments. One way of investigating withdrawal in a controlled environment is to subject smokers to a period of acute abstinence and compare their cognitive performance in this state to their performance in a satiated state. In a systematic review of the literature we identified several cognitive tasks sensitive to a period of acute abstinence (Grabski et al., under review).

We are now attempting to validate and extend these initial findings by replicating tasks used in the literature with an adequate sample size, and investigating methods that have previously not been widely used but are promising. Tasks of interest include the delay discounting, n-back, go/no-go and dot probe tasks. For the latter, eye-movements towards smoking stimuli will be recorded as dwell times have been shown to be more sensitive to abstinence cues than reaction time measures (Field, Mogg, & Bradley, 2004).

We also want to extend the measure of craving of abstinent and satiated smokers over the course of a day. Nicotine withdrawal is known to be dynamic and complex, and fluctuates over time. It is therefore is not well captured by a single assessment (Adams & Munafò, 2013; Bedi et al., 2011; Hughes, 2007). We will use ecological momentary assessment to measure craving of participants via an Android mobile device at several time points over the course of a single day, as participants are in their natural environment.

Study Objectives and Hypothesis

We propose to examine the effects of acute abstinence on cognition and craving in regular smokers. The principal research questions to be addressed are:
1) Is cognitive performance influenced by a period of acute abstinence in smokers?

We hypothesize that abstinent smokers will display changes in performance on the cognitive tasks. Specifically, we predict: preference for smaller, more immediate rewards over larger, longer-term rewards on the delay discounting task; higher number of commission errors on the n-back task and the go/no-go tasks; and, a greater bias towards smoking-related cues on the dot probe task.

2) How is craving affected over the course of the day?

Craving will be assessed via ecological momentary assessment. We hypothesise that tonic craving (i.e., mean levels of craving across the measurement period) will be higher in abstinent smokers, and correlated with measures of cognitive performance. Phasic craving on the other hand (i.e., number and intensity of episodes of peak craving) is predicted to be more frequent in abstinent than in satiated smokers.

**Study Design**

This study is a human laboratory-based study examining the effects of a period of acute abstinence in regular smokers on cognitive measures of working memory, impulsivity and craving over time, using a within-subjects design.

Participants will attend two laboratory sessions. Before one session, participants will be asked to abstain from smoking overnight and until the end of the testing day (abstinent condition). For the other session, participants will be asked to smoke as normal (satiated condition). The order of the conditions will be randomized across participants. On each testing day, the behavioural assessments will be completed in the morning, with the order of the four cognitive computer-tasks randomised across participants and fixed within participants. After testing, participants will be provided with an Android mobile device to measure craving for another six hours, using a specifically programmed app. The assessment of craving can be done remotely, so participants can leave the testing site. After six hours participants will be asked to return the mobile device to the researcher and, in the abstinent condition, have their abstinence confirmed via breath test.

**Study Site**

School of Experimental Psychology, University of Bristol, 12a Priory Road, Bristol BS8 1TU, United Kingdom.

**Participants and Recruitment**

We will recruit 70 individuals aged 18 to 60 years, who are regular smokers from the staff and students of the University of Bristol and from the general population.

Participants will be recruited by existing email lists, posters, flyer advertisement, and by word of mouth. After contacting the research coordinator and reading the study information sheet, participants will complete an initial online screening form. Those who meet the inclusion and exclusion criteria will be contacted by the research co-ordinator to arrange a testing session. Participants will be reimbursed £80 for their time and expenses.

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Inclusion criteria

- 18-60 years old
- smoke at least 5 cigarettes per day
- smoke first cigarette within one hour of waking
- smoking for at least 6 months
- English as first language (or equivalent level of fluency)
- visual acuity within normal limits
- willingness to abstain from smoking for one of the sessions for about 20 hrs., without using any cessation remedies (e.g., nicotine patch, lozenges etc.)

Exclusion criteria

- currently taking any psychoactive medication
- actively trying to give up smoking
- history of substance/alcohol misuse or dependence (other than nicotine or cannabis)
- if female: pregnant, breast feeding or trying to conceive

Sample size determination

We will require 70 participants to achieve 80% power at an alpha-level of 5%, in order to detect the smallest effect size indicated in our recent meta-analysis (d = 0.34 for the delay-discounting task) (Grabski et al., under review). The smallest effect size available was used in order to provide the most conservative sample size estimate. For the cognitive task with the largest effect size (d = 0.59 for the n-back task), a sample size of 25 participants would suffice (Mendrek et al., 2006).

Withdrawal of participants

Participants will be made aware that they can drop out of the research study at any time.

Randomization

The order of sessions (abstinent, satiated) will be randomized. The order of the cognitive tasks during the laboratory session will be randomized across participants, and fixed within participants.

Measures and Materials

Measures

- working memory performance (number of commission errors) as measured by the n-back task
- cognitive bias (dwell time and reaction times) as measured by an eye-tracking dot probe task
- reward choice (area under the curve; AUC) as measured by the delay-discounting task
• tonic and phasic craving measured via ecological momentary assessment using a mobile device

Materials

Questionnaires

Questionnaire measures will comprise the Fagerström Test of Nicotine Dependence (FTND) (Heatherton, Kozlowski, Frecker, & Fagerström, 1991), the Readiness to Quit Ladder (Biener & Abrams, 1991) and the Questionnaire of Smoking Urges - Brief (Tiffany & Drobes, 1991).

Delay-discounting task

Participants are made aware at the start of the task that the amounts of money will be hypothetical and no real money will be gained in this task. Participants are asked to make 91 choices between a standard hypothetical amount of money (£100) available after one of five delays (0, 7, 30, 90, or 180 days) and one of 23 alternative hypothetical amounts available immediately (“Which would you prefer: £100 in 180 days or £30 now?”). Question order is randomized.

N-back task

Participants are required to decide whether each stimulus in a sequence matches the one that appeared n items ago. A 2-back condition will be used. Eight phonologically distinct letters will be used as stimuli (B, F, H, K, M, Q, R, or X). Response time and accuracy of responses will be recorded. The experiment will comprise four blocks, which will consist of 48 trials and an additional practice block of 20 trials. Each trial begins with a central fixation cross, presented for 500 ms, followed by the stimulus in that location for 500 ms and a 2000 ms inter-stimulus interval. Participants will be asked to make a “yes”/“no” response via button press as quickly and accurately as possible.

Go/no-go task

Participants are required to make a response (press button) when a designated “go” cue is presented and withhold responding to a designated “no-go” cue. At the start of each trial a fixation cross is displayed for 500 ms. The cues will be shapes (arrow or star) presented in the centre of a screen for 1000 ms. A practice phase of 6 trials will be implemented, where participants will receive feedback on their performance. The first 20 trials will be go-trials to build a pre-potent response and the remaining 90 trials will be made up of 30 no-go trials and 60 go-trials, presented in randomized order.

Dot-probe task

Participants are presented with two stimuli (photographs), one of which is neutral and one of which is related to smoking. Each trial starts with a central fixation cross, shown for 1000 ms, which is followed by a side-by-side presentation of a pair of the stimuli for 2000 ms. 120 main trials will be presented, of which 80 will be critical trials, including a neutral and a smoking related picture and 40 will be filler trials including neutral pictures only. After presentation of the pictures a dot will appear on one side of the screen, in the former location.
of one of the two pictures. Participants are instructed to indicate the location of the dot as fast as possible via button press. Eye-movements towards these locations on the screen will be recorded from the start of the fixation cross until a button press has been made. There will be 14 practice trials before the start of the main trials.

Ecological momentary assessment

After completion of the laboratory testing session participants will be given an Android mobile device with ecological momentary assessment software installed on it. The software will randomly alert participants over the next six hours to respond to the following questions:

- Able to focus? (yes, no)
- Alert? (yes, no)
- Angry/frustrated? (yes, no)
- Bored (yes, no)
- Calm/relaxed? (yes, no)
- Difficulty concentrating? (yes, no)
- Enthusiastic? (yes, no)
- Happy? (yes, no)
- Irritable? (yes, no)
- Miserable? (yes, no)
- Nervous/tense? (yes, no)
- Quiet/sleepy? (yes, no)
- Restless? (yes, no)
- Sad? (yes, no)
- Cigarette craving? (yes, no)

- Overall feeling? (very bad, bad, neutral, good, very good)
- Arousal/energy level? (very bad, bad, neutral, good, very good)

Participants will furthermore be asked to indicate the highest craving they experienced since the last prompt.

Procedures

Participants will be scheduled to arrive in the laboratory between 8.00 a.m. and 10.00 a.m. Two appointments will be scheduled, at least one week apart. Upon arrival at the first session, participants will be given the opportunity to read the information sheet and ask any questions about the study. The researcher will verbally confirm the schedule of the study and will remind them that they can stop the study at any time without having to give a reason. The participant will complete two copies of the informed consent form, one of which they are able to take away and the other will be filed in the study master file. Participants’ breath CO level will be measured and participants will then complete the questionnaires.

Abstinent session: Participants will be asked to refrain from smoking from midnight before the testing day up to six hours after testing (approximately 20 hours in total). Upon arrival in the laboratory, CO levels will be tested with a breathalyser in order to confirm abstinence.
Satiated session: Participants will be asked to smoke as normal prior to the session, and to smoke a cigarette immediately before testing (to standardise withdrawal), with a maximum delay of 20 minutes between the last cigarette and the start of the session.

Following this, participants will be subjected to the four tasks in randomized order. After the completion of two tasks a break is scheduled in which participant in the satiated condition are asked to smoke a cigarette outside. In the abstinent condition a ten minute break will be scheduled in which participants are offered a glass of water.

After completion of the behavioural assessments, participants will be provided with a mobile device and instructed how to use the mobile device application in order to assess craving. They will be asked to remotely indicate craving levels on the device whenever they are prompted to do so. Craving will be assessed at random intervals for six hours. Participants will be instructed to bring the device back to the testing site at the end of this period, where continued abstinence will be tested via breath test (in the abstinent condition) and participant will complete the questionnaire of smoking urges- brief (Tiffany & Drobes, 1991) once more. Participants will then be debriefed and reimbursed £80 for their time and expenses.

Statistical Plan

Delay-discounting task

Indifference points will be derived and will be used to calculate area under the curve (AUC), using the following equation: \((x_2 - x_1)[(y_1 + y_2)/2]\), where \(x_2\) and \(x_1\) represent successive delays to receiving the standard and \(y_1\) and \(y_2\) the indifference point values associated with these delays. Smaller AUC values indicate greater discounting and impulsive choice (Ashare & Hawk Jr, 2012; Mitchell, 1999). The principal statistical analysis will be a one-way ANOVA of AUC values, with abstinence (abstinent, satiated) as a within-subjects factor.

N-back task

The principal statistical analysis will be a one-way ANOVA of commission error data, with abstinence (abstinent, satiated) as a within-subjects factor.

Go/no-go task

The principal statistical analysis will be a one-way ANOVA of commission error data, with abstinence (abstinent, satiated) as a within-subjects factor.

Dot-probe task

The principal statistical analysis will be a 2 by 2 repeated measures ANOVA of eye movement dwell time data, with picture type (smoking, neutral) and abstinence (abstinent, satiated) as within-subjects factors.

Ecological momentary assessment

We will derive a measure of tonic (i.e., mean) and phasic craving (i.e., number and intensity of episodes of peak craving) using the results from the six random assessments. These measures will be analysed using Generalized Estimating Equations in order to determine
differences between the abstinent and the satiated conditions and correlations to laboratory measures.

**Ethical Considerations and Informed Consent**

Ethics approval has been obtained from the Faculty of Science Research Ethics Committee at the University of Bristol. The study will be conducted according to the revised Declaration of Helsinki (2013) and the 1996 ICH Guidelines for Good Clinical Practice E6(R1). The investigator will explain the nature, purpose and risks of the study to the participant. The participant will receive the information sheet in advance of the study session. There will be no time restriction on how long participants take to respond, with the exception that participants who respond after all study places have been filled will not be offered a place on the study. Therefore, participants will be given sufficient time to read the information and consider any implications, and to raise any questions with the investigators prior to making a decision to participate. Participants will be informed that they are free to withdraw at any time. On arrival at the study session, participants will be given the opportunity to read the information sheet again, and ask any questions. Written informed consent will then be obtained. Participants will be informed that they are free to withdraw at any time.

**Safety**

Discomfort due to cigarette abstinence might be experienced in the abstinence-condition. This will not exceed the discomfort experienced in any regular smoking-cessation attempt for this amount of time.

**Data Management**

All aspects of the Data Protection Act will be adhered to. Consent forms will be retained by the School of Experimental Psychology for a period of 10 years after study completion. In the event that a participant revokes authorisation to collect or use personal health information, the investigator retains the ability to use all information collected prior to the revocation of participant authorisation.

**Anonymised study data**

The case report forms (CRFs) and data will be anonymised by a unique numeric identifier and stored in a locked office. All data requested on the CRF will be recorded. All missing data will be explained. If any entry errors are made, a single straight line will be drawn through the incorrect entry and the correct data entered above it; to correct such an error. All such changed will be initialled and dated. Once data from CRFs have been inputted into a data spreadsheet they will undergo a reliability check (20% check by independent researcher). After the data have been positively assessed, the CRFs will be destroyed in the school’s confidential waste facility.

Original computer data files will be backed up immediately on a secured University of Bristol network drive. At the end of the study, electronic study data (including finalised data sheet) will be transferred to a designated University of Bristol Research Data Storage Facility. Study data will be kept for 5 years after study closure. At the appropriate time the data sheets will be locked and made open using the University of Bristol Data Repository.
Screening documents and participant contact details

Screening documents and participant names and contact details will be stored separately in a study master folder and kept confidential. These will be kept in the study master folder for one year after study completion or until data are made open (whichever comes first), after which these documents will be destroyed. Failed screening documents will be shredded immediately using the School’s confidential waste facility.

Revoked data

If a participant decides that they do not want their data used after their participation they have the right to request that the data are withdrawn. They can request this up to one year after study completion or until the data are made open (whichever comes first).

Quality Control and Quality Assurance

The investigators will be responsible for data quality. After approximately 20% of the data collection has been completed, the study will undergo an in-house quality assessment. During this monitoring process all CRFs and study documents will be assessed as well as the investigators laboratory management and participant engagement, and corrected when necessary.

Insurance

This study will be sponsored by the University of Bristol. The university has Clinical Research Insurance to cover the liability of the university to research participants. In the event that something goes wrong and a participant is harmed during the research study, there are no special compensation arrangements. If a participant is harmed and this is due to someone’s negligence then they may have grounds for a legal action for compensation against Bristol University or one of the other parties to the research, but they may have to pay their own legal costs.

Publication policy

The findings from this research study may be published in an appropriate scientific journal (and made available open access) and/or presented at an appropriate meeting. Study data will be collected and held by the study investigators. The data will be made available for sharing via the University of Bristol online data repository.

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References


