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Running Head: Human Screening Model of Tobacco Abstinence

The development and validation of a human screening model of tobacco abstinence

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Abstract

Introduction Given the low efficacy of smoking cessation methods, an experimental medicine model indicating smoking abstinence would be of great benefit to the development of new treatments. Hence the sensitivity of cognitive tasks and ambulatory craving measures to smoking abstinence were investigated.

Methods Cognitive tasks and ambulatory ratings of craving were assessed for sensitivity to acute abstinence (experiment 1), and nicotine replacement therapy administration (NRT) (experiment 2).

Results In experiment 1 go/no-go performance was improved (Mean Difference [MD] -0.99, 95% CI: -1.90 to -0.08) and craving was lower (Regression Coefficient [RC] -33.39, 95% CI: -39.96 to -26.82) in satiated compared with abstinent smokers. There was no clear evidence that N-back (MD 0.64, 95% CI: -0.42 to 2.51), delay discounting (MD 0.01, 95% CI: 0.001 to 0.005) or dot probe performance (MD 0.61, 95% CI: -0.87 to 1.54) were sensitive to acute abstinence. In experiment 2 go/no-go performance was improved (MD 1.12, 95% CI: 0.16 to 2.08) and craving was lower (RC -18.59, 95% CI: -24.63 to -12.55) smokers abstinent overnight receiving NRT compared with placebo. There was no clear evidence that N-back (MD -0.25, 95% CI: -1.45 to 0.94), delay discounting (MD 0.01, 95% CI: -0.002 to 0.004) or dot probe performance (MD -0.49, 95% CI: -1.61 to -0.64) were sensitive to NRT.

Conclusions Findings from two experiments converge to suggest that abstinence in smokers reliably increases ambulatory craving assessments and, to a lesser extent, decreases go/no-go task performance. These findings can be utilized in the development of an experimental medicine model to test novel treatments for smoking cessation.

Keywords: tobacco withdrawal, tobacco abstinence, cognitive performance, ecological momentary assessment, smoking cessation, experimental medicine model

The development and validation of a human screening model of tobacco abstinence

1. Introduction

Most smokers are aware of the negative health consequences of smoking, but many are unable to quit even when using the best treatments currently available (Cahill et al., 2013). Although the need for novel treatments is clear, their development is expensive and time-consuming. Experimental medicine models allow for the assessment of efficacy of novel compounds in healthy volunteers in a cost- and time-effective way (Lerman et al., 2007).

Cognitive tasks might be able to inform about specific performance deficits during abstinence and could furthermore act as a precise objective measure of changes to the abstinence state. Moreover, there is a wealth of literature on smoking abstinence and cognitive impairment (Munafo et al., 2003, Myers et al., 2008, Ashare and Hawk, 2012, Leventhal et al., 2010, Park et al., 2000, Field et al., 2004). We previously reviewed the literature on the effect of acute abstinence on cognitive tasks ("acute abstinence studies") and whether cognitive tasks can predict cessation attempt outcomes ("cessation studies") (Grabski et al., 2016). The design of cessation studies was too heterogeneous to permit meta-analysis, hampering definite conclusions about the predictiveness of cognitive tasks on cessation outcomes. In acute abstinence studies extensive variation in the tasks, methods and quality of study design were found as well, yet seven tasks were common enough in order to be meta-analysed. Meta-analyses revealed the following tasks to be sensitive to acute abstinence: delay discounting, response inhibition, recognition memory and mental arithmetic tasks, whereas several attentional bias measures based on manual reaction times were not (Grabski et al., 2016).

Furthermore, cigarette craving might be a promising treatment target as it predicts (and may cause) relapse (Killen and Fortmann, 1997, Piper et al., 2011). However, several issues

need consideration when assessing cigarette craving as an indicator of abstinence. First, it is not well captured by the assessment of one single time point (Adams and Munafo, 2013); second, retrospective assessments are prone to memory bias (Shiffman, 2009); third, the ability of craving to predict relapse is influenced by the abstinence state of the smoker (Gass et al., 2014); and, fourth, the evidence is mixed regarding the sensitivity of craving to approved smoking cessation medications, such as nicotine replacement therapy (NRT), in short-term laboratory procedures (Teneggi et al., 2002). Some of these pitfalls can be avoided by the employment of ecological momentary assessment (EMA) methods, where participants are equipped with a portable device that collects information in their natural environment (Shiffman and Stone, 1998, Stone and Shiffman, 1994), as this would allow for the repeated, real-time assessment of craving (Shiffman et al., 2002, Shiffman and Waters, 2004). However, the risk of self-report bias remains. We therefore propose a screening model for tobacco abstinence including both, ambulatory measures of craving combined with cognitive performance measures, acting as a precise objective validation of the self-report measures

The identification of objective measures of smoking status in combination with ambulatory craving assessments could be used to develop a time efficient screening model for novel smoking cessation treatments and could furthermore inform research efforts to use enhancement of cognitive performance as a treatment intervention (Sofuoglu et al., 2013, Ashare et al., 2014).

Informed by our previous meta-analysis we set up a test battery including the following tasks: a delay discounting task (assessing impulsive decision making), a response inhibition task (assessing impulsive action), an N-back task (assessing working memory), an eye-tracking dot-probe task (assessing attentional bias), an additionally EMA measures of craving severity. As we were previously not able to synthesise evidence on cessation studies we decided to focus on overnight abstinence only (Grabski et al., 2016).

In experiment 1, we manipulated acute withdrawal, and hypothesized that smokers would display worse working memory performance, impaired response inhibition, greater delay discounting and greater attentional bias towards smoking related cues over neutral cues in acute abstinence as compared to smoking satiety. In experiment 2, we compared abstinent smokers receiving active nicotine replacement therapy (NRT)—a treatment known to effectively reduce withdrawal symptoms and craving—in one session and placebo NRT in the other. We hypothesised that measures sensitive to acute abstinence in experiment 1 would be normalised in the active condition compared to placebo.

2. Experiment 1

2.1. Methods

2.1.1. Participants

Participants were recruited from the general population. Participants were required to be between 18-60 years of age, have normal visual acuity, smoke a minimum of 5 cigarettes a day, smoke for at least 6 months and smoke within the first hour of waking. Exclusion criteria were currently trying to give up smoking, pregnancy, currently breast feeding or trying to conceive, the use of psychoactive medication, and a response of ‘no’ to the following statement: “I have no current or previous substance or alcohol misuse or dependence (other than nicotine and cannabis)”. Approval was granted by the Faculty of Science Research Ethics Committee at the University of Bristol.

2.1.2. Materials

Participants completed four tasks – a go/no-go task (assessing impulsive action through manual reaction times) (Hindocha et al., 2018) a delay discounting task (assessing impulsive decision making through decisions on hypothetical monetary rewards delay) (Hindocha et al.,

2018), an N-back task (assessing working memory of letters), a dot probe task (assessing attentional bias through eye-movements) (Field et al., 2004) and an EMA procedure to assess cigarette craving (Schüz et al., 2013) (for a detailed description of the tasks see Supplementary Material 1).

2.1.3. Procedure

Participants attended two test sessions, approximately one week apart. For one session participants were asked to abstain from smoking from midnight before the test day and throughout the day, while for the other session they were asked to smoke as they usually would. In this way participants in the abstinent condition would be abstinent for a minimum of 8 hours at the start of the laboratory session. The laboratory session lasted approximately two hours and was scheduled to begin in the morning between 8 – 11 am. The order of the two sessions was counterbalanced across participants. In the abstinent condition, abstinence from smoking was confirmed with a breath carbon monoxide (CO) sample reading of ≤10 ppm at the start of the laboratory session and at the end of the test day. If a participant arrived to the abstinent session with a higher CO than the cut-off point the session was cancelled and re-arranged, if possible. In the satiated condition participants were asked to smoke a cigarette 20 minutes before the start of the laboratory session, in order to standardize baseline nicotine levels.

Following these procedures, readiness to quit (Contemplation Ladder) (Biener and Abrams, 1991), dependence (Fagerström Test of Cigarette Dependence, FTCD) (Heatherton et al., 1991) and craving (Questionnaire of Smoking Urges-Brief, QSU-Brief) (Cox et al., 2001) were assessed, after which participants completed the test battery, with the tasks randomized across and constant within participants. After the completion of two tasks participants were asked to take a short break. In the satiated condition participants were instructed to smoke a cigarette outside during the break, in order to prevent withdrawal. After the completion of the remaining test battery participants were provided with a mobile telephone device, which had

custom software running the EMA programme. They were instructed on how to use the device and to bring it back in the late afternoon (4-6 hours later). Participants in the abstinent condition were reminded to abstain from smoking until that time. On return to the laboratory participants were asked to provide another carbon monoxide reading and craving was assessed once more.

2.1.4. Statistical Analysis

Seventy participants were required to achieve 80% power and an alpha-level of 0.05 in order to detect the smallest effect size for the tasks included (d = 0.34 for the delay discounting task) as indicated by a meta-analysis of cognitive tasks sensitive to abstinence (Grabski et al., 2016).

For the go/no-go data, commission errors, omission errors and reaction times in the abstinent and satiated condition were analysed using dependent-samples t-tests. It was hypothesized that commission errors (i.e., false positives) would increase under acute abstinence, as previously reported (Grabski et al., 2016).

For the N-back data, commission errors, omission errors and reaction times in the abstinent and satiated condition were analysed, using dependent-samples t-tests. It was hypothesised that omission errors (i.e., false negatives) would increase under acute abstinence (Grabski et al., 2016).

For the delay discounting task data, the logged discounting parameter k (Odum, 2011) was derived from the indifference points from abstinent and satiated smokers and analyzed using a dependent-samples t-test. It was hypothesised that discounting would increase under acute abstinence (Grabski et al., 2016).

For the dot probe task data, only critical trials were analyzed for both dwell time and bias scores of first saccades. First saccades were analyzed only if the saccade originated from the fixation cross in the center of the screen, this was the case for 88% of all saccades averaged

across abstinent and satiated sessions. Overall dwell time as well as bias scores of first saccades were each analyzed using a 2 × 2 repeated measures ANOVA. Picture type (smoking, neutral) and abstinence (abstinent, satiated) were included as a within-subject factors for the analyses of both. It was hypothesised that abstinent smokers would spend more time looking at smoking pictures over neutral pictures than satiated smokers (Field et al., 2004).

For the EMA data, differences in craving measures between the abstinent and satiated state in the remote assessment component were analyzed using Generalized Estimating Equations (GEE). GEE are designed to account for the auto-correlation of data in repeated-measures designs (Zeger et al., 1988).

All analyses were conducted using R statistical software (Foundation for Statistical Computing, Vienna, Austria). The study protocol was pre-registered at the Open Science Framework (https://osf.io/5qgys/). The data that form the basis of the results presented here are available here: http://data.bris.ac.uk/data, doi XXXX.

2.2. Results

2.2.1. Characteristics of Participants

We recruited 70 participants (29 female, 41%), with an average age of 21.8 years (SD 5.0). The average FTCD score was 4.4 (SD 1.7) (Heatherton et al., 1991), participants reported they smoked 11 (SD 3.8) cigarettes per day and had a Contemplation Ladder score of 4.0 (SD 0.9) . Due to technical error test battery results of one participant were lost as well as the results of two participants for the N-back task and the delay discounting task. Similarly, we were only able to obtain dot probe eye-tracking data for 60 participants. The EMA assessments from five participants were missing for at least one of the two sessions and therefore excluded.

The final analysis of the sample therefore comprised 69 participants for the go/no-go task, 67 participants for the N-back and the delay discounting tasks, 60 participants for the dot probe task and 65 for the EMA assessment.

CO sample readings were markedly lower in the abstinence than in the satiated condition, confirming that participants adhered to the abstinence protocol ($t[69] = 4.6$, $p<0.001$). The QSU-Brief results show that participants experienced higher cravings during the abstinent than during the satiated condition. ($t[69] = 4.8$, $p<0.001$) (see Table 1).

2.2.2. Go/no-go task

There was evidence for higher commission error rates in the abstinent condition than in the satiated condition ($t[68] = -2.16$, $p = 0.034$) (see Table 2). Ad-hoc analysis revealed that there were no session – order effects for go/no-go task performance or ambulatory craving assessments. Go/no-go commission error rates and ambulatory measures of craving were not associated (RC = 0.002, $p = 0.628$), nor were go/no-go commission error rate and a craving x condition interaction (RC = <0.001, $p = 0.918$).

2.2.3. N-back task.

There was no clear evidence for a difference omission errors in the abstinent and satiated condition ($t[66] = 1.42$, $p = 0.16$) (see Table 2).

2.2.4. Delay discounting task.

There was no clear evidence of a difference between the logged values of the discounting parameter k in the abstinent and satiated conditions ($t[66] = 1.24$, $p = 0.25$) (see Table 2).

2.2.5. Dot probe task

There was evidence of a main effect of dwell time on picture type ($F[1, 59] = 53.87$, $p < 0.0001$), with more time spent looking at smoking over neutral pictures, but no clear evidence of a main effect of session ($F[1, 59] = 0.01$, $p = 0.91$), or of a picture × session interaction effect ($F[1,59] = 0.30$, $p = 0.58$). The analysis of first saccade towards the stimuli revealed a main effect of dwell time on picture type ($F[1, 59] = 55.45$, $p<0.0001$), but no evidence of a main effect of session ($F[1, 59] = 0.32$, $p = 0.57$), or of a picture × session interaction effect ($F[1,59] = 0.87$, $p = 0.35$) (for mean differences see Table 2).

2.2.6. Ecological momentary assessment

Each participant received about 4.4 prompts (SD 1.35) per session and the duration between first and last prompt was 3.85 hours (SD 1.49) on average. The number of prompts received did not differ greatly between conditions (N[abstinent] = 298, N[satiated] = 305). Compliance was good with 92% of prompts answered, more prompts were missed in the satiated condition (N[abstinent] = 19, N[satiated] = 33). The mean craving score in the abstinent condition was 75.0 (SD 24.1) and in the satiated condition 41.3 (SD 28.6). The mean craving score for the very first prompt received was 74.93 (SD) in the abstinent condition and 44.70 (SD 28.68) in the satiated condition.

Smoking condition (abstinent versus satiated) was found to be highly predictive of craving levels (RC = -33.39, $p<0.0001$) when included as the only predictor of craving in the model. Time (minutes since midnight) was not found to predict craving when added to the model (RC = 0.02; $p = 0.160$). There was weak evidence for an abstinence × time interaction term (RC = -0.04; $p = 0.061$). The decrease of the effect of condition on craving in model 3 is likely due to multicollinearity, which inflated the standard error (see Table 3).

2.3. Discussion Experiment 1

Response inhibition performance on the go/no-go task and ambulatory craving levels were sensitive to acute abstinence in regular smokers, whereas N-back, delay discounting and dot probe eye-tracking performance were not. In experiment 2, we investigated whether these results would be echoed when comparing abstinent smokers randomised to receive active NRT versus placebo.

3. Experiment 2

3.1. Methods

Methods were identical to those in experiment 1 unless indicated otherwise. Approval was granted by the Faculty of Science Research Ethics Committee at the University of Bristol.

3.1.1. Procedure

Participants attended two sessions about 1 week apart. On both sessions participants had to abstain from smoking from midnight before the test session until the end of the testing day, requiring to abstain for a minimum of 8 hours before the start of the session. In one session participants received an NRT patch (14 mg) and nasal spray (10 mg/ml), on the other session a matching placebo patch and spray (Rusan Pharma, Ltd.). The order of the two sessions was counterbalanced across participants, and participants were blind to treatment condition. The two sessions were identical in procedure: They were scheduled to begin in the morning between 8 – 11 am. The patches were applied to the participants' arm at the beginning of the test session, then they were asked to use the nasal spray once. A 30-minute break was scheduled, to ensure sufficiently high blood levels of nicotine before the laboratory assessments. The laboratory

assessment lasted about 2 hours. After the completion of the laboratory assessments participants were instructed to use the spray throughout the day whenever they experienced cravings. On return to the test-site the patch was removed, the nicotine spray collected and times of use of the spray recorded.

3.1.2. Statistical Analysis

Analysis procedures were identical to those described for Experiment 1. The study protocol was pre-registered at the Open Science Framework (https://osf.io/apsjx/). The data that form the basis of the results presented here http://data.bris.ac.uk/data, doi XXXX.

3.2. Results

3.2.1. Characteristics of participants

We recruited 70 participants (38 female, 54%), with an average age of 22.5 years (SD 6.3). The average FTCD score (Heatherton et al., 1991) was 3.4 (SD 1.5), participants reported that they smoked 9.3 cigarettes per day (SD 3.5) and had a Contemplation Ladder score (Cox et al., 2001) of 4.4 (SD 1.0) (see Table 1).Participants in the placebo condition reported using the nasal spray 1.41 times on average and in the active condition 0.78 times over the course of the afternoon (Table 1).

Four participants dropped out of the study because they were unable to tolerate the treatment. These participants were replaced. On all occasions this was during the active NRT condition, and all four participants named nausea as the main reason for deciding to discontinue. Their daily intake was on average 8.7 cigarettes (SD 1.8), and thus only slightly lower than the average of the overall study sample.

The results of one participant for the delay discounting task, three participants for the go/no-go and the N-back tasks, and seven participants for the eye-tracking task were missing due to technical error. For the EMA assessment data from eight participants were missing for at least one of the two sessions and therefore excluded. The final sample for analysis therefore comprised 69 participants for the delay discounting task, 67 participants for the N-back and the go/no-go task, 63 participants for the dot probe task and 62 for the EMA assessment. The results of the QSU-brief indicate that craving levels were comparable in both treatment conditions in the morning but increased in the afternoon only in the placebo condition, whereas they decreased slightly in the NRT condition (see Table 1).

3.2.2. Pharmacological intervention

The mean use of placebo nasal spray was 1.41 times (SD=1.0) and of the active nasal spray 0.78 (SD=0.84). Several participants reported the sensation of the active nasal spray to be unpleasant. The patch generally seemed to be tolerated well. Participants guessed administration of active NRT correctly most of the time (80%), but were less accurate when guessing allocation of placebo (60%).

3.2.3. Go/no-go task

There was evidence for higher error rates in the placebo condition than in the active NRT condition ($t[66] = 2.32$, $p = 0.024$) (see Table 4.). Ad-hoc analysis revealed that there were no session – order effects for go/no-go task performance or ambulatory craving assessments. Go/no go commission error rates and ambulatory measures of craving were not associated (RC = 0.010, $p = 0.192$), and neither were go/no-go commission error rate and a craving x treatment interaction (RC = 0.002, $p = 0.828$).

3.2.4. N-back task

There was no clear evidence of a difference between omission errors in the active NRT and placebo condition (t[66] = 0.42, p = 0.67) (see Table 4).

3.2.5. Delay discounting task

For the delay discounting task, there was no clear evidence of a difference between the logged values of the discounting parameter k in the active NRT and placebo conditions (t[68] = 0.66, p = 0.51) (see Table 4).

3.2.6. Dot probe task

There was strong evidence of a main effect of dwell time on picture type (F[1, 62] = 22.67, p < 0.0001), with more time spent looking at smoking over neutral pictures and of a main effect of session (F[1, 62] = 8.11, p = 0.006), with participants in the placebo condition spending more time looking at pictures regardless of type. There was no clear evidence of a picture × session interaction effect (F[1,62] = 0.73, p = 0.40). There was strong evidence of a main effect of picture type on direction of first saccade (F[1, 62] = 13.14, p < 0.001), but no clear evidence of a main effect of session (F[1, 62] = 0.05, p = 0.82), or of a picture × session interaction effect (F[1,62] = 1.10, p = 0.31) (for mean differences see Table 4).

3.2.7. Ecological momentary assessment

Each participant received about 4.3 prompts (SD 1.70) per session and the duration between first and last prompt was 3.52 hours (SD 1.51) on average The number of prompts received did not differ greatly between conditions (N[placebo] = 269, N[active NRT] = 257). Compliance was good with 89 % of all prompts answered, more prompts were missed in the placebo than in the active condition (N[placebo] = 31, N[active] = 21). The mean craving score

in the placebo condition was 73.5 (SD 20.4) and in the NRT active condition 54.4 (SD 27.5). The mean craving score for the very first prompt received was 74.72 (SD 20.45) in the placebo condition and 50.88 (SD 8.85) in the active NRT condition.

Treatment condition (active NRT versus placebo) was found to be highly predictive of craving levels (RC = -18.59, $p < 0.0001$) when included as the only predictor of craving in the model, with those in the NRT group reporting significantly lower levels of craving. Time was also found to weakly predict craving when added to the model (RC = 0.01, $p = 0.013$), by slightly increasing. There was weak evidence for an effect of the condition × time interaction term (RC = 0.02, $p = 0.066$). The decrease of the effect of treatment on craving in model 3 is likely due to multicollinearity, which inflated the standard error (see Table 5).

3.3 Discussion

Our go/no-go data indicated that commission error rate is sensitive to nicotine administration during smoking abstinence, while our EMA data indicated that ambulatory measures of cigarette craving are highly sensitive to nicotine administration during acute abstinence. There was no clear evidence that the N-back, delay discounting or dot probe task performance were sensitive to treatment.

4. General Discussion

The effects of changes to the abstinence state on cognitive task performance and craving in smokers were investigated in order to support the development of a human screening model of smoking abstinence. We found an increase in craving during acute abstinence in experiment 1 and during placebo NRT administration in experiment 2. We furthermore found a decline in go/no-go task performance during acute abstinence in experiment 1 and during administration of placebo NRT in experiment 2, even though this effect was much smaller. Delay discounting,

working memory and attentional bias task performance were not found to be sensitive to either acute abstinence or nicotine administration.

The increase of ambulatory ratings of cigarette craving during tobacco abstinence and decrease during NRT administration is in line with previous findings (Shiffman et al., 2006). This supports the assumption that craving levels assessed by EMA might be more sensitive to NRT in a short-term abstinence setting than when assessed using other methods (Teneggi et al., 2002). However, contrary to our expectations we did not find a strong effect of time on craving levels in the abstinent condition in experiment 1 and in the placebo condition in experiment 2. One potential explanation for this is that craving levels might have reached a ceiling at the start of the EMA, due to the relatively late start in the day of the EMA assessment and the smoking cues used in the preceding task battery. This is supported by the observation that the first craving levels recorded were already close to mean craving levels in both the abstinent condition in experiment 1 and the placebo condition in experiment 2.

The decrements found on the go/no-go task in abstinent smokers are likely a result of impaired response inhibition rather than general cognitive impairments, as we only found the hypothesized difference between conditions in commission error rates and no difference on other measures, such as reaction times or omission errors (Smith et al., 2014) in both experiments. Our finding that attentional bias, measured via eye-movements, was not affected by acute abstinence is consistent with previous findings showing that attentional bias measures for substance-related cues have poor internal reliability (Ataya et al., 2012). The fact that the effect of abstinence on go/no-go performance was relatively small and that none of the other cognitive measures, identified by a systematic review of the literature, were affected by acute abstinence aligns with conclusions from our previous work: research on acute abstinence and cognitive performance should give higher priority to statistical power and focus on the replication of results (Grabski et al., 2016).

Interestingly go/no-go performance and craving levels were not associated with each other. This could be due to the fact that they represent different abstinence phenotypes, but generally the two measures described should be compared with caution as there were considerable differences both in the number of assessments (single vs multiple time points) as well as the assessment methodology (lab-based vs experience sampling).

The effect of abstinence was much more pronounced for measures of craving than for go/no-go performance in both experiments. Despite this we would argue for retaining both of these components in the model: Firstly, the difference in magnitude might partially be driven by the differences in assessment method discussed above. Secondly, and more importantly, an objective validation of self-report measures is a crucial addition to a treatment screening model, especially given the difficulty of adequately blinding non-pharmacological as well as pharmacological treatments (Bello et al., 2016). Arguably an objective performance measure is not as likely to be influenced by participants correctly guessing treatment allocation as a subjective performance measure.

Future studies might investigate ambulatory assessments of craving, and potentially other measures related to smoking withdrawal such as negative affect or stress, as well as go/no-go task performance, which will allow for a better comparisons between the two model components. Furthermore, well-controlled studies assessing the relationship between the model components and smoking cessation outcomes would increase the model's ecological validity. This could inform on whether increasing go/no-go task performance to aid cessation, similar to efforts of decreasing craving, might be a worthwhile target for interventions as proposed previously (Ashare et al., 2014; Sofuoglu, DeVito, Waters, & Carroll, 2013).

A particular strength of this series of experiments is the agnostic approach taken in the set-up of the cognitive task battery. The decision on which tasks to include was preliminarily based on findings from a previous systematic review, making the rationale comprehensible and

objective. Given the lack of a predominant theory predicting and explaining how specific cognitive domains might be affected during tobacco abstinence this was considered the ideal procedure to identify cognitive tasks reliably sensitive to changes in the withdrawal state.

For both experiments the following limitations apply: First, the short-term design of both experiments does not allow conclusions about whether any of the changes observed actually relate to subsequent smoking cessation, which should be addressed in further research. For example, the current findings could be combined with a longer term experimental medicine model of abstinence, such as developed by Perkins and colleagues (Perkins et al., 2006). Second, the inclusion criterion of a minimum of five cigarettes smoked per day might have caused a sample with relatively low tobacco dependence, which could have influenced the results, as task performance decrements have been found to be exacerbated in heavier smokers (Sweitzer et al., 2008). Third, the inclusion of less demanding versions of performance tasks, such as a 1-back version of the N-back, next to the 2-back version could have elucidated whether sensitivity to abstinence was associated with task difficulty. Fourth, screening for medication or recreational drug use was done via self-report only. Furthermore recent use of permitted drugs (eg. cannabis) was not recorded. Fifth, both studies were not double-blind. The first experiment did not allow for the blinding of neither participants nor the researcher, and in the second experiment only participants were blinded to the NRT condition. Furthermore, we were not able to tailor the nicotine dose according to the dose participants were accustomed to. Thus, for some participants the dose might have been either too high or too low, both of which could result in decrements of task performance, introducing uncontrolled error to the results. Related to the previous point, the exclusion of four participants (5% of those tested) due to adverse reactions to the active NRT might have introduced bias to our sample as smokers who are able to tolerate the treatment in combination with lengthy laboratory test sessions might also differ on other aspects from the general smoking population. Lastly, the current study design does not allow for an investigation

on whether changes in task performance were due to withdrawal or an 'offset effect' (Hughes, 2007) (i.e., sustained changes following drug cessation, rather than the transient effects of withdrawal). Whether the effects of abstinence are transient is difficult to determine in a short-term study. Nevertheless, whether the changes in go/no-go task performance and craving observed are a direct result of withdrawal or an offset effect should not affect the value of our findings as they could both drive relapse, and could therefore act as an indicator of treatment results.

Novel smoking cessation treatments are an important way to improve population health. Our findings from two separate experimental studies converge to suggest that go/no go task performance as well as ambulatory cravings assessments are reliably sensitive to acute abstinence in smokers. Future studies should investigate whether these changes in the abstinent state are predictive of smoking cessation success. This model might then be utilized to preliminarily screen novel smoking cessation methods.

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Table 1. Participants' Smoking Characteristics.

Experiment 1	Satiated		Abstinent		Effect Size (*d*)	p-value
	M	SD	M	SD		
CO (ppm)						
Morning	15.62	5.6	7.73	2.65	1.64	<0.0001
Afternoon	14.35	6.02	5.27	2.89	1.75	<0.0001
QSU-Brief						
Morning						
QSU Total	16.10	9.95	26.06	9.02	1.04	<0.0001
QSU Factor 1	18.72	10.32	31.97	8.59	1.38	<0.0001
QSU Factor 2	13.48	10.64	20.14	10.70	0.63	<0.0001
Afternoon						
QSU Total	19.39	11.58	31.13	7.99	1.17	<0.0001
QSU Factor 1	22.55	12.30	36.81	6.42	1.27	<0.0001
QSU Factor 2	16.23	12.05	25.88	11.24	0.83	<0.0001

Experiment 2	Placebo		NRT		Effect Size (*d*)	p-value
	M	SD	M	SD		
CO (ppm)						
Morning	6.66	2.57	5.75	2.98	0.22	0.063
Afternoon	4.61	2.70	3.21	2.39	0.10	0.398
NS use	1.41	1.00	0.78	0.84	-	-
M check	64	-	84	-	-	-
QSU-Brief						
Morning						
QSU Total	26.95	7.65	26.33	7.38	0.10	0.388
QSU Factor 1	20.17	8.50	19.34	7,73	0.13	0.286
QSU Factor 2	33.74	8.46	33.31	8.49	0.06	0.636
Afternoon						
QSU Total	22.85	5.70	28.69	7.08	0.89	<0.0001
QSU Factor 1	14.92	4.83	22.14	8.18	0.92	<0.0001
QSU Factor 2	30.78	8.09	35.25	0.76	0.62	<0.0001

CO: carbon dioxide, ppm: parts per million, NS: nasal spray, M check: manipulation check (% correct).

Table 2. Test Battery Results (Experiment 1).

	Satiated		Abstinent		Effect Size	95% CI	p
	M	SD	M	SD	(*d*)		
Go/no-go							
CE	1.68	1.97	2.67	3.90	0.29	-1.89, -0.08	0.034
OE	0.09	0.41	0.19	0.79	0.15	-0.26, 0.06	0.211
RTs (sec)	0.83	0.06	0.83	0.08	0.09	-0.01, 0.02	0.471
Delay Discounting							
Log (*k*)	0.013	0.023	0.012	0.018	0.10	-0.001, 0.005	0.250
N-Back							
CE	5.85	7.42	6.60	7.39	0.22	-0.49, 1.97	0.228
OE	5.33	5.36	6.37	5.97	0.17	-0.42, 2.51	0.160
RTs (sec)	1.31	0.69	1.30	0.64	0.02	-0.11, 1.10	0.868
Dot Probe							
Dwell Time*	2.35	3.69	2.69	3.39	0.07	-0.87, 1.54	0.584
Direction 1st Saccade*	5.67	8.50	6.97	8.48	0.12	-1.48, 4.07	0.353

* m and sd values represent mean difference (smoking vs neutral pictures); p-values represent interaction of picture x session; CE: Commission errors, OE: Omission Errors.

Table 3. Results: Craving and Abstinence (EMA Experiment 1).

	[1]			[2]			[3]		
	RC	SE	p	RC	SE	p	RC	SE	p
Condition	-33.39	3.34	<0.0001	-33.21	2.15	<0.0001	-2.53	16.67	0.87
Time				-0.02	0.01	0.16	0.04	0.03	0.19
Condition-time							-0.04	0.02	0.06

[1]: model including main variable “condition”, (no. observations: 584), [2]: model including main variables “condition” and “time”, (no. observations: 575), [3]: model including main variables “condition”, “time” and a “condition-time” interaction term (no. observations: 575), Condition: abstinence vs. satiation, Time=minutes since midnight. (abstinent [1], satiated [2])

Table 4. Test Battery Results (Experiment 2).

	NRT		Placebo		Effect Size (*d*)	95% CI	p
	M	SD	M	SD			
Go/No-Go							
CE	2.17	2.96	3.29	4.55	0.28	0.16, 2.08	0.024
OE	0.02	0.17	0.02	0.17	0.00	-0.06, 0.06	1.000
RTs (sec)	0.36	0.06	0.36	0.06	0.03	-0.01, 0.01	0.832
Delay Discounting							
Log(k)	0.01	0.02	0.01	0.01	0.08	-0.002, 0.004	0.509
N-Back							
CE	6.74	9.31	5.21	8.05	0.20	-0.30, 3.37	0.100
OE	5.85	4.54	6.10	5.76	0.05	-1.45, 0.94	0.673
RTs (sec)	1.14	0.56	1.17	0.54	0.07	-0.14, 0.08	0.566
Dot Probe							
Dwell Time*	1.41	2.27	0.92	3.50	0.11	-1.61, 0.64	0.396
Direction 1st Saccade*	4.27	10.05	2.60	9.65	0.13	-4.90, 1.57	0.308

* mean and sd represent mean difference (smoking vs neutral pictures); p-values represent interaction of picture x session; CE: Commission errors, OE: Omission Errors.

Table 5. Results Craving and Treatment (EMA Experiment 2).

	[1]			[2]			[3]		
	RC	SE	p	RC	SE	p	RC	SE	p
Treatment	-18.59	3.08	<0.001	-18.62	3.04	<0.001	-34.41	9.05	0.0001
Time				0.01	0.01	0.013	-0.01	0.01	0.267
Treatment-time							0.02	0.01	0.066

[1]: model including main variable “treatment”, (no. observations: 515), [2]: model including main variables “treatment” and “time”, (no. observations: 515), [3]: model including main variables “treatment”, “time” and a “treatment-time” interaction term, (no. observations: 515), Treatment: placebo vs. NRT, Time: minutes since midnight. (placebo [1], active NRT [2])