# Cannabidiol reverses attentional bias to cigarette cues in a human experimental medicine model of tobacco withdrawal.

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# Abstract

Current pharmacological treatments for smoking cessation have limited efficacy and can produce significant side effects. Cannabidiol (CBD), the non-intoxicating cannabinoid, may be a promising novel smoking cessation pharmacotherapy with anxiolytic properties and minimal side effects. This randomized, double-blind crossover laboratory study utilised an experimental medicine approach to investigate whether CBD would reduce withdrawal symptomology, salience and liking of cigarette cues following overnight abstinence in dependent cigarette smokers. Thirty non-treatment seeking, dependent, cigarette smokers attended three sessions. The first was a fixed satiated session, followed by two overnight abstinent sessions in which they were randomised to receive either 800mg oral CBD or placebo (PBO). Compliance on all sessions was biologically verified. Their reactivity to pictorial tobacco cues was recorded using an attentional bias task and an explicit rating task. Withdrawal, craving, side effects, heart rate and blood pressure were assessed at multiple timepoints. Tobacco abstinence increased attentional bias when participants were treated with placebo (*p*=.001, *d* =.789) compared to satiation. However, CBD reversed this effect, such that automatic attentional bias was directed away from cigarette cues (*p*=.007, *d:* .704) and no longer differed from satiety (*p=*.82). CBD reduced explicit liking of cigarette images, compared to placebo (*p=.036*). Craving and withdrawal were greater in abstinence and unaffected by CBD. Systolic blood pressure decreased under CBD during abstinence. In the first study to investigate CBD for nicotine withdrawal, our results highlight a reduction in the salience of drug cues as a key neurocognitive mechanism through which CBD may assist with the treatment of tobacco and other substance use disorders.

# Introduction

# Over 1.1 billion people smoke worldwide (WHO, 2015). Although this number is decreasing in the western world (Frazer et al. 2016), it is still estimated that six million people will die per year due to cigarette smoking. A primary addictive driver of cigarette smoking is nicotine withdrawal. Withdrawal occurs upon cessation and includes physiological symptoms (headaches, nausea), affective symptoms (anxiety, depression and irritability) and impaired cognitive performance (delay discounting, response inhibition) (Grabski *et al*, 2016) which peak within the first few days (Hughes, 2007). Some evidence suggests withdrawal severity predicts relapse (Hughes, 2007; Killen and Fortmann, 1997; Patterson *et al*, 2010; Piasecki *et al*, 2003), prevention of which is one of the greatest challenges in the treatment of addiction (Potenza *et al*, 2011). Even when using the most effective smoking cessation drug (varenicline), a majority still fail to maintain long-term abstinence (Schnoll and Lerman, 2006). Nicotinic medications may also have unpleasant side effects e.g. weight gain (Cahill *et al*, 2016).

There is mounting evidence that the endogenous cannabinoid (eCB) system is involved in motivation for rewards including modulating the rewarding effects of drugs (Hindocha *et al*, 2017b; Lawn *et al*, 2016; Parsons and Hurd, 2015; Prud'homme *et al*, 2015; Zlebnik and Cheer, 2016). In relation to nicotine dependence, antagonists of the CB1 receptor, e.g. rimonabant, decrease nicotine conditioned place preference (CPP), self-administration (Forget *et al*, 2005; Le Foll and Goldberg, 2004) and in human clinical trials, rimonabant has been shown to increase abstinence rates by 1.6 times (Cahill and Ussher, 2011; Robinson *et al*, 2017). Although potentially effective, rimonabant was withdrawn from the market due to serious neuropsychological side effects.

Cannabidiol (CBD) is the second most abundant cannabinoid in cannabis and has broad therapeutic benefits; its mechanism of action is diverse, incompletely elucidated, and includes antagonism at 5-HT receptors (Campos and Guimarães, 2008; Zanelati *et al*, 2010) and a partial agonism at dopamine D2 receptors (Seeman, 2016). It increases extracellular anandamide by Fatty Acid Amide Hydrolase (FAAH) inhibition (Bisogno *et al*, 2001; De Petrocellis *et al*, 2011). Interestingly, inhibiting anandamide reuptake decreases nicotine CPP and possibly self-administration in rats (Gamaleddin *et al*, 2011; Scherma *et al*, 2012 however see Merritt et al., (2008) for enhanced nicotine CPP in FAAH knockout mice). CBD has a low affinity to the CB1 receptor (Pertwee, 2008) and this is unlikely to the candidate mechanism for its actions.

The psychological properties of CBD are suggestive of a potentially ideal drug for smoking cessation. These include its lack of intoxicating and subjective effects (Babalonis *et al*, 2016; Haney *et al*, 2015; Hindocha *et al*, 2015), antipsychotic (Leweke *et al*, 2012; Leweke *et al*, 2015; Schubart *et al*, 2014) and anxiolytic (Bergamaschi *et al*, 2011; Fusar-Poli *et al*, 2009) effects in humans. Its anxiolytic properties may be particularly relevant, as anxiety is a primary symptom of tobacco withdrawal (Hughes, 1992). The first human pilot study to investigate CBD as a treatment for nicotine dependence randomised participants to either one-week of ad-hoc CBD or placebo inhaler and were instructed to use it when they had the urge to smoke. CBD reduced the number of cigarettes smoked by almost 40% (Morgan *et al*, 2013). This preliminary study did not investigate any neurocognitive mechanisms through which CBD may assist with the treatment of smoking cessation. However, on the basis of previous findings, the authors proposed a reduction in the salience of drug cues could be one candidate mechanism.

Attentional bias is an important in-lab predictive marker of the salience of drug cues, it is heightened during acute abstinence (albeit weakly in meta-analysis, due to multiple methodologies : Grabski *et al*, 2016), predicts short-term relapse (Waters *et al*, 2003) and is thought to play a causal role in addiction (Franken, 2003). The short exposure interval is particularly important as tobacco abstainers show greater salience to drug cues only in the short exposure (Freeman *et al*, 2012). CBD may reduce the salience of smoking cues which would be consistent with preclinical and human neuroimaging research (Ren *et al*, 2009). In human naturalistic research, cannabis with high, in comparison to low, levels of CBD reduced cue salience to cannabis-related stimuli in a visual probe task (Morgan *et al*, 2010). This was only observed at the short stimulus exposure interval which taps ‘automatic’ bias, i.e. that which is not subject to conscious cognitive control. As such, CBD may target an important process in relapse and have a role as an adjunct cessation pharmacotherapy. Ren et al. (2009) showed CBD (5–20 mg/kg) attenuated cue-induced heroin seeking behaviour and relapse (during active heroin intake) in a rat model of addiction which was significant even two weeks after CBD administration. Furthermore, human pilot research showed a single dose of CBD can attenuate cue-induced craving in heroin users and was maintained for 24 hours (Hurd *et al*, 2015). Neuroimaging has elucidated that CBD modulates activity of areas in the brain highly associated with different aspects of salience attribution including the striatum, hippocampus and prefrontal cortex (Bhattacharyya *et al*, 2015). Therefore, there is a strong rationale to examine CBD as a potential treatment for tobacco and other substance use disorders where the salience of cues is key.

The present study utilises an experimental medicine approach to investigate CBD’s potential to target processes relevant to smoking cessation. Human laboratory studies of smoking abstinence provide an efficient, cost-effective, mechanistic evaluations of medications for smoking behaviour (Lerman *et al*, 2007), which may further help facilitate translational research. This is the first study to investigate CBD for nicotine withdrawal in humans. We hypothesised that ~12-hour nicotine abstinence, relative to satiety, would produce a range of symptoms consistent with nicotine withdrawal in dependent cigarette smokers, specifically, increased craving and withdrawal, greater attentional bias in the short exposure and liking of cigarette related stimuli. Secondly, we hypothesised that CBD in comparison to placebo, would attenuate craving, withdrawal symptomology, attentional bias and liking of cigarette related stimuli.

# Material and Methods

## Design and participants

Thirty participants attended 3 sessions (7.85 ± 2.77 days between sessions). Participants smoked as normal before their first (baseline) session, verified with expired Carbon Monoxide (CO) ≥ 10 p.p.m (Bedfont Scientific, Harrietsham, UK). Participants then attended two sessions after overnight (~12 h) abstinence, verified by CO ≤ 10ppm (Benowitz *et al*, 2002). A double-blind placebo-controlled crossover design was implemented to investigate the effects of 800mg oral CBD, in comparison to placebo (PBO), after overnight abstinence. Treatment order for abstinent sessions was randomised and counterbalanced.

Dependent cigarette smokers were recruited from the local community and through online message boards. Inclusion criteria were: i) age 18-50 years, ii) smoking ≥10 cigarettes a day for at least the last year, iii) FTND score ≥ 4 (moderate dependence) (Heatherton *et al*, 1991), iv) smoking first cigarette within an hour of waking, iv) negative drug urine screen for all drugs on the first session. Exclusion criteria were: i) use of nicotine replacement therapy or any other nicotine pharmacotherapy, ii) self-reported recent use of cannabis or other illicit drugs, iii) recent (past 4 weeks) or on-going use of e-cigarettes, iv) current mental or physical health issues or learning impairments v) pregnancy or breast feeding vi) allergies to cannabidiol, gelatine, lactose, microcrystalline cellulose or chocolate.

## Power calculation

We calculated an N of 20 would be necessary to have power of 0.95 to detect a large effect size of d=0.78 (F=0.38). This was based on the difference in the number of cigarettes smoked pre- to post- one week of CBD inhaler vs. placebo in Morgan et al. (2013). This sample size was increased by 50% to adjust for “winner’s curse”, or the tendency for effect sizes estimates from an initial positive finding to be over-inflated (Button *et al*, 2013) yielding a final sample of 30.

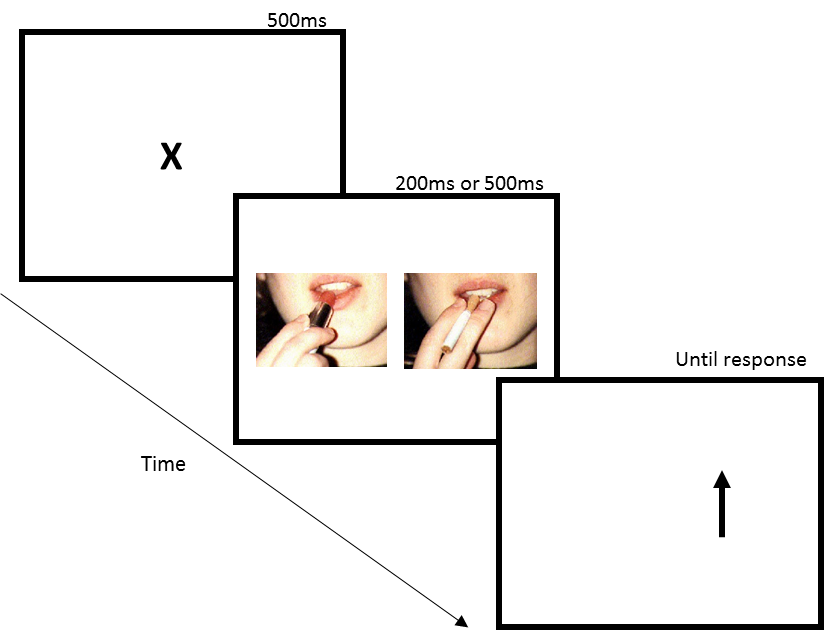
## Drug administration

Participants were administered 800mg oral CBD doses (pure synthetic (-)-CBD, STI Pharmaceuticals, Essex, England) or matched placebo (lactose powder) in capsules in a double-blind, counterbalanced manner. The 800mg dose was chosen as it has shown efficacy for schizophrenia, increased extracellular anandamide levels (Leweke *et al*, 2012), and should be sufficient to influence salience attribution after a single dose (Bhattacharyya *et al*, 2015). 800mg produces an increase in plasma concentrations after administration (Cmax = 77.9 ±25 ng/mL, Tmax=180 minutes ).

## Assessments

### Visual probe task

This task was implemented as a measure of attentional bias, adapted from Charles *et al* (2015). The smoking (target) and composition-matched neutral (non-target) images were taken from Mogg *et al* (2003) who provide a complete description of the stimuli. Each trial began with a fixation point (500 ms). A pair of images then appeared on the left and right of the screen for either a short (200 ms) or long (500 ms) duration to assess automatic orienting and controlled attention processing, respectively. Image pairs were then replaced by a probe (an arrow pointing upwards or downwards) in the location of either the neutral or smoking related image. The probe remained on screen until the participant responded to identify the probe orientation (upwards or downwards) by pressing one of two appropriate response keys (k/m) as quickly and accurately as possible. Probes replaced the cigarette-related and neutral images equally often. The right/left position of image type, probe location, and stimulus duration were counterbalanced. Trials were displayed in a single block, with each pair presented eight times, producing 80 critical trials and 32 neutral trials. The task began with 4 buffer trials. Trial order was randomised each time the task was run. The task was programmed with Experiment Builder (SR Research, Ontario, Canada).



*Fig 1. Trial structure for the visual probe task. Example of cigarette (right) and matched neutral stimuli (left) provided*

### Pleasantness Rating Task (PRT)

This task tapped explicit liking and reaction time to the same pictures used in the visual probe task. Each trial began with a fixation cross of 500ms, followed by either a cigarette or neutral cue, presented in a randomised order for 3000ms. Stimuli were matched on brightness and complexity. Stimuli for cigarettes involved smoking-related scenes were the same as the visual probe. Participants rated the pleasantness of each image on a scale of -3 (very unpleasant) to +3 (very pleasant). Two dependent variables of valence and reaction time were recorded. 3 versions were available for counterbalancing. The experiment was built and conducted using Psychopy (Peirce, 2007, 2009).

## State questionnaires

Withdrawal was assessed with the Mood and Physical Symptoms Scale (MPSS) (West and Hajek, 2004). Craving was assessed with Questionnaire of Smoking Urges–Brief (QSU-B) (Tiffany and Drobes, 1991). Participants completed a 6-item Side Effect form for CBD which included “strong drug effect”, “good drug effect”, “willing to take drug again”, “like drug effect”, “I have an upset stomach” and “I have a headache”. Each item was rated 3 times over abstinent sessions on a 10 point visual analogue scale from “not at all” to “extremely”.

## Trait Questionnaires

The Fagerström test for Nicotine Dependence (FTND) was used to assess nicotine dependence (Heatherton *et al*, 1991). Anxiety was assessed with the Trait Anxiety Inventory (STAI; (Spielberger *et al*, 1970)). Depression was assessed with Beck Depression Inventory (BDI-II; (Beck *et al*, 1961). A comprehensive drug history was also taken (Hindocha *et al*, 2017a). Premorbid Verbal Intelligence was assessed with the Spot The Word Task (Baddeley *et al*, 1993).

## Procedure

After telephone screening, eligible participants attended a baseline ‘satiated session’ prior to which they smoked as normal. This involved further screening assessments (urine test, pregnancy test, spot the word) as well as the same assessments as on the abstinent days. On the satiated day, participants completed state measures of craving (QSU-B) and withdrawal (MPSS), were asked to smoke a cigarette (Marlboro Gold) at the beginning of the session to ensure satiation then completed the task battery. On abstinent sessions, participants attended two 3.5 hour sessions separated by one week after overnight abstinence. They provided a CO reading then completed state questionnaires (QSU-B, MPSS). CBD or matched placebo was then orally administered. After drug administration, participants completed half the trait questionnaires in each session. At 1h (T1) and 2h (T2) after drug administration, they again completed the MPSS and QSU-B. At 2.5 hours, they completed the visual probe and PRT. At 3.5h after drug administration, participants completed the MPSS and QSU-B (T3). All participants provided written informed consent. Ethical approval was given by UCL Ethics Committee. Participants were reimbursed £10/hour.

## Statistical analysis

Statistical analyses were performed in the Statistical Package for Social Scientists (SPSS 21; IBM, Chicago, IL). Visual inspection of diagnostic plots was used to check for normality. Outliers > 1.5 x the interquartile range (IQR) were winsorized to the next highest value. For the PRT, 4.2% of the data was missing due to technical issues and were replaced with the means of the condition.

The visual probe, PRT, MPSS and QSU were analysed using repeated measures ANOVA with two *a priori* orthogonal Helmert contrasts to investigate main effects. The first describes the main effect of abstinence i.e. satiated (SAT) vs. abstinent (CBD+PBO), the second describes the main effect of drug i.e. CBD vs. PBO. Interactions were explored via pairwise post-hoc comparisons, Bonferroni-corrected locally within each omnibus term. Task specific factors included exposure time (long, short) for the visual probe, stimulus type (cigarette, neutral) for the PRT-RT. The MPSS and QSU utilised an additional task specific factor of time (T1(pre-drug), T2, T3). Given side effects, HR, systolic and diastolic BP was only taken once on SAT session, these data were analysed with a 2 (CBD, PBO) x 3 (T1 (pre-drug), T2, T3) ANOVA.

Only correct trials were analysed for the visual probe. Responses >2000 and <200ms were removed. Following Mogg *et al* (2005), bias scores were calculated for the visual probe and PRT such that a positive score indicates a bias towards cigarette cues. For the visual probe, this was calculated as the difference in RT between when the probe replaced the neutral in comparison to cigarette stimulus (RT\_neutral – RT\_cigarette); for the PRT-Valence it was calculated as cigarette\_valence – neutral\_valence.

# Results

## Participant characteristics

30 participants (14 female) took part. Demographics and trait measures can be found in table 1. Use of other drugs was minimal in this population (table 2).

*Table 1. Participants’ demographic and trait variables.*

|  |  |
| --- | --- |
| n | 30 |
|  |  |
| Age | 28.07 (8.66) |
| FTND score | 5.56 (1.13) range 4-8 |
| Cigarettes per day | 13.5 (2.39) range 10-20 |
| Time to first cigarette (mins) | 25.50 (15.87) |
| Years smoked | 9.55 (7.36) |
| Years smoking >10+ cigarettes/day | 8.17 (7.08) |
| Lifetime quit attempts (n=25) | 3.20 (3.91) |
| Most Successful quit attempt (days) | 100.48 (163.47) |
| BMI | 23.98 (7.78) |
| Spot the Word | 48.03 (4.15) |
| STAI | 40.53 (9.40) |
| BDI | 10.36 (7.54) |

## Drug use

*Table 2: Drug use history (N = the number of people who used the drug in the past year).*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Alcohol | Cannabis | MDMA | Cocaine |
| N | 26 | 14 | 9 | 9 |
| Last used (days) | 6.39 (10.13) | 100.00 (68.30) | 84.66 (82.22) | 100.00 (56.12) |
| Years used | 13.08 (8.68) | 8.29 (4.61) | 4.55 (1.59) | 3.33 (2.12) |
| Days per month | 11.43 (8.85) | 0.75 (1.30) | 0.67 (1.32) | 0.5 (1.15) |
| Amount per session | 7.10 units (3.23) | 0.87 joints (0.69) | 258.33mg (144.70) | 800mg (0.83) |

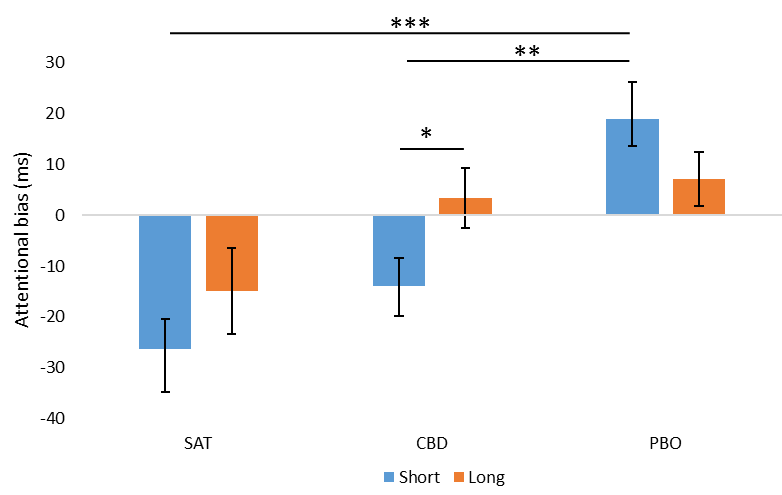
## Manipulation checks

Self-reported time since last smoked and an objective measure of expired CO both indicate that participants were abstinent on abstinent sessions. For further details see the supplementary materials.

## Attentional Bias

### Visual probe task

We found a condition x exposure interaction (*F*(2,58)=4.66, *p*=.013, ηp2= .138). The interaction showed that under the short exposure, there was greater attentional bias to cigarette cues in the PBO condition, in comparison to SAT (MDiff= 45.15ms (SE: 10.48), *p*=.001, *d*: .789), as well as greater attentional bias in the PBO condition in comparison to CBD (MDiff= 36.47ms (SE: 10.90), *p*=.007, *d:* .704) but not between SAT and CBD (MDiff= -8.68ms (SE: 7.77), *p=*.82). Follow up one-sample t-tests against 0 showed both SAT (t(29)= -4.42, p<.001), and CBD (t(29)= -2.54, p=.017) were more significantly more negative than zero, and PBO was significantly more positive than 0 (t(29)=2.63, p=.014). Under the long condition, none of these comparisons were significant. Additionally, there was a significant difference between short and long exposure times for CBD (MDiff= -20.94 (SE: 8.13), *p*=.015) but not under SAT (*p*=.263) or PBO (*p*=.155). There was a main effect of abstinence (*F*(1,29)=9.52, *p*=.004, ηp2=.274) which showed there was a greater attentional bias under abstinence versus satiation. There was a main effect of drug which was subsumed under the condition x exposure interaction. There was no main effect of exposure time (*F*(1,29)=2.14, *p*=.155 ηp2=.069).



*Figure 2: Attentional bias across each session for both short and long exposure times. Error bars are ±SEM. \* p≤ .05, \*\* p≤ .01, \*\*\* p≤ .001*

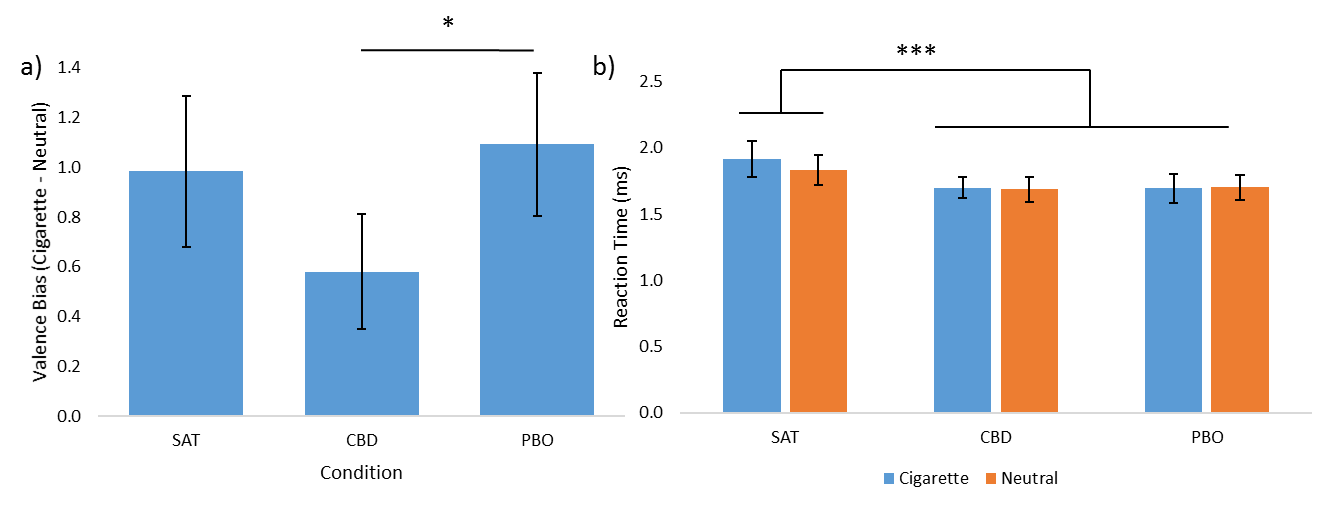
## Pleasantness Rating Task

#### Valence (Fig. 3a)

A one way ANOVA on bias scores (CigValence-NeutralValence) revealed a significant main effect of drug (*F*(1,29)=7.41, *p*=.011, ηp2=.203), indicating a lower bias towards cigarettes images on CBD compared to PBO. There was no main effect of abstinence (*F*(1,29)=0.53, *p*=.472, ηp2=.018).

#### RT (Fig. 3b)

There was a main effect of abstinence (*F*(1,29)=7.41, *p*=.011, ηp2=.204) where participants were slower in the satiated condition (M:1.87, SE:0.11) than in the abstinent sessions (CBD: 1.69, SE: 0.07, PBO: 1.70, SE: 0.08). There was no main effect of drug, stimulus type or drug x stimulus type interaction (*F*(2, 58) =.131, p=.876, ηp2 =.004).



*Figure 3: a) Bias in pleasantness rating (calculated as cigarette valence minus neutral valence) for all three conditions and b) reaction time with the factor of stimulus type included. Error bars are ±SEM. \* p≤ .05, \*\* p≤ .01, \*\*\* p≤ .001*

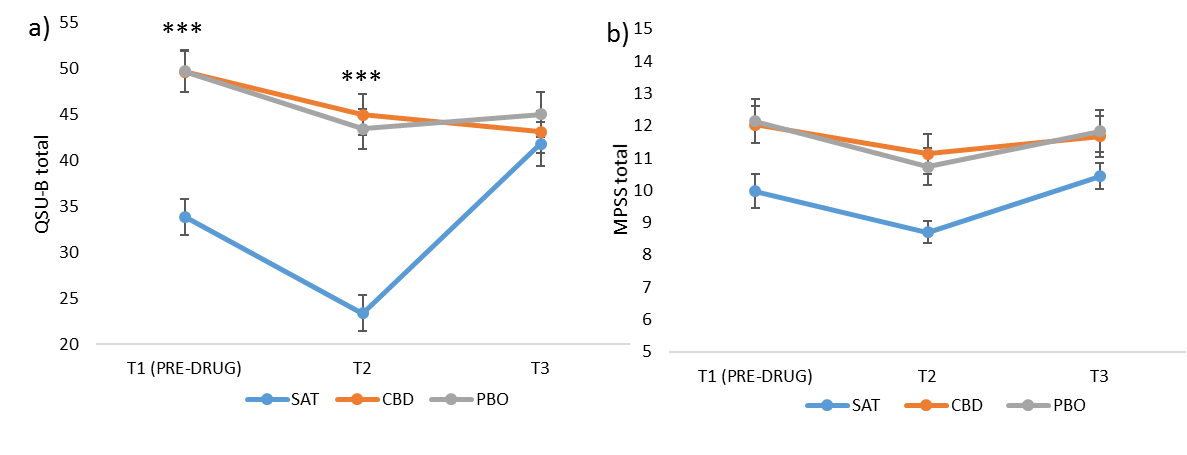
## Craving (Fig 4a)

There was a condition x time interaction (*F*(4,116)=21.38, *p*<.001, ηp2=.424) which was driven by significant differences between satiated and abstinent sessions on the first two time-points (all *p*‘s <.001). At T3, no differences emerged between conditions. There was also a main effect of abstinence (*F*(1,29)=29.92, *p*<.001, ηp2=.51) and time (*F*(1.63,47.31)=20.76, *p*<.001, ηp2=.418). There was no main effect of drug.

## Withdrawal (Fig. 4b)

#### MPSS total

There was a main effect of abstinence (*F*(1,29)=12.04, *p*=.002, ηp2=.293) which showed higher MPSS total scores on abstinence days in comparison to satiated. There was also a main effect of time (*F*(2,58) =11.35, *p*<.001, ηp2=.281) which showed in all sessions that withdrawal decreased at T2 then increased at T3. There was no main effect of drug or condition x time interaction. Analysis from the additional MPSS questions (amount of time spent with urges, and strength of urges) can be found in the supplementary materials.



*Figure 4: Scores for the a) QSU-B (craving) and b) MPSS total (withdrawal) as a function of time and condition. Error bars are ±SEM. \* p≤ .05, \*\* p≤ .01, \*\*\* p≤ .001*

## Cardiovascular

#### Heart rate

There was a main effect of time (*F*(1.35, 39.07) =33.73, *p*<.001, ηp2=.540) which showed HR decreased over time. No other main effects or interactions emerged.

#### Blood pressure

For systolic blood pressurewas a main effect of drug (*F*(1,29)= 6.72, *p*=.015, ηp2=.188) which showed higher blood pressure in the placebo condition (M: 114.16 SE: 1.43) compared to CBD (M: 110.75 SE: 1.463). There was also a main effect of time (*F*(2,58) =13.24, *p*<.001, ηp2=.313) which showed that systolic blood pressure decreased over time. There were no main effects or interactions for diastolic blood pressure.

#### Side effects

There were no main effects of drug or interactions between drug and time for any of the six items. Full analysis can be found in the supplementary materials.

## Correlations

There were no correlations between PRT-Valence and attentional bias or between craving, withdrawal and attentional bias or with trait measures. Trends towards positive and medium-large correlations emerged between bias in valence on the PRT and craving scores (T3) in the SAT (*r*(30)=.46, *p*=.01) and PBO (*r*(30)=.38, *p*=.04) but not for CBD (*r*(30)=.27, *p*=.14).

# Discussion

This study employed an experimental medicine approach to investigate the utility of a single dose of CBD in a laboratory model of nicotine withdrawal. We found evidence that CBD shifted attentional bias away from cigarette cues in comparison to placebo, such that it was no longer significantly different from attentional bias under satiety. Simultaneously, we observed a reduction in explicit liking during abstinence such that cigarette stimuli were rated as less pleasant after CBD than placebo. These neurocognitive effects occurred in the absence of any changes in subjective states such as craving and withdrawal between CBD and placebo. This suggest that CBD may have specific effects on the evaluative and motivational-salience reducing properties of drug cues which is consistent with clinical (Hurd *et al*, 2015; Morgan *et al*, 2010) and preclinical (Ren *et al*, 2009) research. Moreover, no side-effects or psychoactive or significant cardiovascular effects were noted. These results support the potential of CBD it the treatment of addictive disorders.

A reduction in the implicit salience of drug cues of a large effect size was observed in the CBD condition (vs. placebo) after overnight abstinence in dependent cigarette smokers. That is to say that participants were faster to detect probes replacing smoking (vs. control) cues under placebo. This was observed in the short exposure time only, consistent with our hypothesis and with previous findings that smokers of high CBD:THC cannabis strains had a reduced attentional bias to both cannabis and food stimuli in at a short (but not long) exposure compared to those who had a low CBD:THC ratio (Morgan *et al*, 2010). The short exposure time to related to implicit automatic processing and initial orientation to cues, and less likely to do with awareness than the long attentional bias (Field and Cox, 2008) which may be why it did not correlate with explicit liking or questionnaire measures of craving and withdrawal.

These results suggest that the mechanism by which CBD exerts its observed anti-addictive effects are early and directly on the normalisation of the salience of drug cues and is in line with the incentive salience model of drug addiction (Robinson and Berridge, 2001). Previous research using the visual probe tasks has also highlighted a role of automatic attentional bias in tobacco dependence, showing sensitivity to tobacco abstinence (Freeman et al., 2012) and acute administration of a dopamine D2/D3 agonist (Freeman et al., 2015). Given that attentional bias may predict smoking cessation outcomes (Waters *et al*, 2003), CBD may be useful in aiding early abstinence by reducing the salience of drug-related cues.

The neurobiological mechanism by which CBD may exert these effects is unclear, however a promising candidate is through normalisation of extracellular anandamide, via inhibition of FAAH. FAAH inhibitors have been shown to reduce nicotine self-administration and CPP in rats and monkeys as well as nicotine-induced dopamine release in the nucleus accumbens (Forget *et al*, 2009; Justinova *et al*, 2015; Panlilio *et al*, 2013; Scherma *et al*, 2008). Here, we were unable to collect anandamide levels, however this putative mechanism requires further research as more potent FAAH inhibitors may provide more anti-addictive effects than CBD. This also may be the mechanism by which CBD may alleviate psychotic symptoms in people with schizophrenia (Leweke *et al*, 2012). Interestingly, there may be a common biological substrate that underlying both smoking and psychosis which involves changes in salience attribution or ‘aberrant salience’ (Freeman *et al*, 2014; Kapur, 2003). Indeed previous research suggests CBD modulates activity in the areas of the brain associated with salience attribution during an attentional salience task (Bhattacharyya *et al*, 2012; 2015).

As well as effects of CBD on implicit attentional bias, we saw a reduction in explicit liking for cigarettes under CBD in comparison to placebo. Explicit liking is important in regards to addiction because it partly indexes the reinforcing value of a drug. Users of high, in comparison to low, CBD: THC ratio cannabis showed lower self-reported liking of cannabis stimuli which follows the same pattern as the present study (Morgan *et al*, 2010) and may be related to endocannabinoid involvement in hedonic experiences (Mahler *et al*, 2007). However, there was no difference between abstinence and satiated sessions as we had hypothesised, and has previously been shown (Field *et al*, 2004). Moreover, in this study, we found trends towards positive medium sizes correlations between valence and craving but only for the satiated and placebo session, but not under CBD, thus adding validity to the PRT and likely because both are explicit measures.

## Limitations

This study has some limitations. Firstly, we used an experimental medicine approach to investigate mechanistic effects of single dose CBD during tobacco withdrawal therefore it is unclear whether these effects will translate to the clinic and how long the effects last. The visual probe task only provides a cross-sectional snapshot of attentional bias at a specific time point in a laboratory setting, and in this case Ecological Momentary Assessment may be more indicative of attentional bias in actual drug taking environments. Additionally, use of eye tracking, fMRI and/or EEG would have provided additional information on the time course and neural correlates of attentional bias. Moreover, only a single dose of CBD was given; future research needs to investigate the repeated dosing and a range of doses (Zuardi *et al*, 2017). Finally, compliance with abstinence instructions were based on self-report, therefore we could not verify that participants had not used other nicotine products, apart from cigarettes (verified with CO), however, craving and withdrawal scores were markedly higher under abstinence than satiation suggesting this was not the case.

## Conclusions

In conclusion, this study shows that after overnight tobacco abstinence, cigarette smokers given CBD, in comparison to placebo show a reduced salience of cigarette cues and reduced liking of cigarette cues, in the absence of any reductions in withdrawal or craving. This study highlights the potential utility of CBD as a treatment for tobacco and other substance use disorders and suggests that one mechanism by which CBD may exert its effects on addiction is via a reduction in salience of drug cues.

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