Interactions between Cannabinoids and Tobacco: Implications for understanding and treating addictive disorders.

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I, Chandni Hindocha, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Cannabis and tobacco are two of the most commonly used drugs in the world and their use often co-occurs. Cigarette smoking continues to be a global epidemic where novel drugs for smoking cessation are necessary. In **chapter 1,** I review the literature concerning cannabis, tobacco and co-used cannabis and tobacco, in relation to their prevalence and effects on cognition, addiction and psychosis. In **chapter 2,** I provide a 'worldwide' overview of routes of administration (ROA) of cannabis with and without tobacco (n=33, 687). Tobacco-based ROAs were most common in Europe (77.2–90.9%) and Australasia (20.7–51.6%) but uncommon in the Americas (4.4–16.0%). Tobacco-based ROAs were associated with reduced motivation to quit tobacco. In **chapter 3**, I describe the first investigation of the individual and interactive effects of cannabis and tobacco in a randomized, placebo-controlled, double-blind crossover design (n=24). I found tobacco may offset effects of cannabis on delayed recall, had no effect of cannabis-induced psychotomimetic or subjective effects and was more harmful for cardiovascular outcomes. In **chapter 4,** in the same sample, I found tobacco did not influence the rewarding effects of cannabis. In **chapter 5,** in the same sample, I developed an innovative "roll a joint" paradigm to assess quantity of both drugs. I found self-reported quantity was accurate for tobacco but overestimates cannabis exposure. In **chapter 6 and 7,** in a sample of overnight-abstinent dependent cigarette smokers (n=30), I investigated if cannabidiol (CBD) can reduce nicotine withdrawal. Results showed CBD reduced attentional bias and pleasantness ratings but increased errors on the go/no-go, compared to placebo. There were no effects on verbal episodic, working memory or delay discounting. Finally, in **chapter 8,** I summarise and integrate my findings into the literature, discuss implications, consider limitations and suggest future research on the interaction between cannabinoids and tobacco.

Impact statement

The research in this thesis has significantly added to the knowledge about the interaction between cannabis and tobacco by providing the first experimental study of their interaction utilising the world's most popular method of consumption: joints with tobacco. This research has been disseminated through four high impact papers. Implications for public health include providing evidence to challenge the commonly held beliefs about tobacco in cannabis joints. Data in this thesis regarding "cannabis vaping" also constitutes 5% of research on PubMed to date (May 2018) on this phenomenon. Results were disseminated in national and international news including The Guardian and The Daily Mail and reached young cannabis users through websites such as Vice. It has contributed to the national and European discourse regarding the potential effects of cannabis legalisation – for example, it has been used by think tanks. I further reported the results to public health officials of the National Committee for the Prevention and Control of Tobacco in Spain. Implications of these results will be in public health and policy design regarding legalisation of cannabis in Europe. Furthermore, this thesis has prompted further research in co-use and collaborations with national and international academic partners (including a Horizon2020 COST action). Finally and hopefully, this research may provide impetus for a European-wide cultural change in regards to cannabis consumption.

This thesis also provides the first data to provide a mechanism for why cannabidiol (CBD), the non-intoxicating cannabinoid found in cannabis, can be used as a treatment for nicotine addiction. This research has been disseminated through two high impact papers. Additionally, the study won an award at a national conference (Society of the Study of Addiction; best poster prize £200) and international (Society of Biological Psychiatry; predoctoral award $2000 and the International Cannabinoid Research Society; £700) conferences. These two studies represent the second and third papers in existence that experimentally tests the effects of CBD on smoking cessation outcomes. The research was covered by the *I newspaper* and *The Scotsman*. It has been used as

the basis of an InnovateUK grant application, which is a government funding body that connects an academic institution and a business venture. This research will be important for commercial companies looking to bring cannabinoids into the marketplace for addiction treatment as it provides high quality experimental-medicine evidence for the application of a cannabis-based medicine. This can be used to support clinical trials of CBD for smoking cessation. Additionally, since the mechanisms of action for CBD is unknown, this research will provide some impetus for preclinical back-translation to investigate the mechanism of CBD.

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The work presented in this thesis gave rise to the following publications:

- **Hindocha, C.,** Freeman, T.P., Ferris, J.A., Lynskey, M.T., & Winstock, A.R., (2016). No Smoke without tobacco? A global overview of cannabis and tobacco routes of administration and their association with intention to quit. *Frontiers in Psychiatry* 7(104) 1-9.

- **Hindocha, C.,** Freeman, T.P., Winstock, A.R., & Lynskey, M.T. (2016). Vaping cannabis (marijuana) has the potential to reduce tobacco smoking in cannabis users. *Addiction* 111(2) 375 – 375.

- Lynskey, M.T., **Hindocha, C.,** Freeman, T.P. (2016) Legal regulated markets have the potential to reduce population levels of harm associated with cannabis use. *Addiction* 111 2090-2096

- **Hindocha, C.,** Freeman, T.P., Xia Jian X., ShaBan, N.D.C., & Curran, H.V. (2017). Acute memory and psychotomimetic effects of cannabis and tobacco both 'joint' and individually: a placebo-controlled trial. *Psychological Medicine* 47(15) 2708-2719.

- Walsh, H., **Hindocha, C.,** & Duaso, M. (2017). Commentary on Popova et al. (2017): Co-used and co-administered tobacco and cannabis (marijuana) require further investigation. *Addiction* 112 1830-1831.

- **Hindocha, C.,** Lawn, W., Freeman, T.P., & Curran, H.V. (2017). Individual and combined effects of cannabis and tobacco on reward processing. *Psychopharmacology* 234(21) 3153-3163.

- **Hindocha, C.,** Freeman, T.P., & Curran. H.V (2017). Anatomy of a joint: comparing self-reported and actual dose per joint of cannabis and tobacco, and how they are influenced by controlled administration of these drugs. *Cannabis and Cannabinoid Research* 2(1) 217-223.

- **Hindocha, C.,** Norberg, M. M., & Tomko, R.L (2018). Solving the problem of cannabis quantification. *Lancet Psychiatry* 5(4) e8.

- **Hindocha, C**., Freeman, T.P., Grabski, M., Stroud, J.B., Crudgington, H., Davies, A.C., Das, R.K., Lawn, W., Morgan, C.J.A., & Curran, H.V. (2018). Cannabidiol reverses attentional bias to cigarette cues in a human experimental model of tobacco withdrawal. *Addiction* 113(9), 1696-1705.

- **Hindocha, C.**, Freeman, T.P., Grabski, M., Crudgington, H., Davies, A.C., Stroud, J.B., Das, R.K., Lawn, W., Morgan, C.J.A. & Curran, H.V. (2018). The effect of cannabidiol on impulsivity and memory during abstinence in dependent cigarette smokers. *Scientific Reports* 8(1), 7568.

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List of Abbreviations

2-AG	2-arachidonoylglycerol
AKT1	RAC-alpha serine/threonine-protein kinase
APA	American Psychiatric Association
BOLD	Blood Oxygenated Level Dependent
BP	Blood Pressure
CB1R	Cannabinoid Receptor 1
CB2R	Cannabinoid Receptor 2
CBD	Cannabidiol
CBT	Cognitive Behavioural Therapy
CI's	Confidence intervals
CM	Contingency Management
CO	Carbon Monoxide
CPP	Conditioned Place Preference
CPT	Cigarette Purchase Task
CSF	Cerebrospinal Fluid
CUD	Cannabis Use Disorder
DSM-5	Diagnostic and Statistical Manual - 5th Edition
eCB	Endocanninoid
FEP	First Episode Psychosis
FTND	Fagerstrom Test of Nicotine Dependence
GABA	Gamma-aminobutyric acid
HR	Heart Rate
IV	Intervenous
MET	Motivational Enhacement Therapy
MPT	Marijuana/Cannabis Purchase Task
NAcc	Nucleus Accumens
nAChRs	Nicotine Acetylcholine Receptors
NHS	National Health Service
NRT	Nicotine Replacement therapy
NSDUH	National Survey on Drug Use and Health
ONS	Office of National Statisitcs
OR	Odds Ratio
PSI	Psychotomimetic states Inventory
ROA	Route of Administration
RP	Relapse Prevention
STAI	State-trait anxiety inventory
THC	Delta-9-tetrahydrocannabinol
TUD	Tobacco Use Disorder
VTA	Ventral tegmental area
WHO	World Health Organisation

Chapter 1: General Introduction

Cannabis and tobacco are two of the world's most widely used drugs. The consumption patterns of both drugs have had recent dramatic changes in opposite directions however; their combined use remains constant. Cannabis, once demonised, now stands to become a legal drug, equivalent to alcohol and tobacco itself. After decades of halted research, it is also now the basis of novel medications such as Sativex and Epidiolex. On the other hand, cigarette smoking has declined tremendously amongst the general population but there are still groups of vulnerable individuals, such as people with severe mental health problems and substance use disorders (including cannabis use disorder), where the decline has been less dramatic. This is partly because both drugs are often used in combination and 'jointly' have a unique relationship with important psychological and physiological consequences on health and quality of life.

In this introduction, I will review research on cannabis, tobacco and their co-use. Firstly, I will give a brief history of cannabis use and the current state of the legal landscape surrounding this highly controversial drug. I will then review the epidemiology of cannabis use and neurobiology of the endocannabinoid system. I move onto the subjective and psychological effects of its use including the acute effects of cannabinoids on two types of memory: verbal episodic and working memory. I will also review the effects of cannabinoids on psychotic symptoms and addiction, including the effects on reward processing, specifically reviewing the use of purchase tasks as measures of relative reinforcement efficiency. I will end with a review of treatment options, both psychological and pharmacological, available for cannabis dependence.

In the next section, I will briefly review the same topics for tobacco. In the third section, I will review what is known about the combined effects of cannabis and tobacco. I will specifically review terminology for combined use, the current knowledge regarding the epidemiology of co-use and the proposed mechanisms behind why these two drugs which are so often used together, including the gateway hypothesis. Additionally, I will review the limited literature of the cognitive, psychotomimetic and reward-related effects

associated with combined use. Finally, I will review the limited research on treatment options of co-use and issues surrounding measuring cannabis use.

I will then identify a series of questions, which need to be addressed. These questions with form the empirical spine of this thesis.

1.1 Cannabis

Cannabis has a rich and controversial history. It has been used for both medical and spiritual purposes for millennia (Mechoulam et al. 2014; Mechoulam and Parker 2013). The first recorded use of cannabis was in China over 6000 years ago where it was used as hemp - a fibrous material utilised in textiles and for its psychoactive and medical qualities (Zuardi 2006). In ancient Indian, Persian and Arabic societies, it was used in religious rituals and ceremonies (Haney and Hill 2018).

However, at the time of writing this thesis, cannabis is a schedule 1 drug meaning it has no medical use. In the United Kingdom (UK), cannabis is a class B drug putting it in the same class as amphetamines. Currently, those in 8 states (California, Maine, Nevada, Massachusetts, Colorado, Washington, Oregon, and Alaska) and the District of Columbia have legalised cannabis for recreational use and 29 states currently have legal medical cannabis use. In June 2018, Canada legalised recreational cannabis by passing The Cannabis Act. In South America, Uruguay is the only nation to legalise recreational cannabis. Argentina, Chile, Puerto Rico, Columbia and Mexico have decriminalised medical cannabis use. In Europe, the tide is shifting and there is increasing debate on medical and legal cannabis. The Netherlands have maintained tolerated sales in the well-known Dutch “coffee shop” model where they have had decriminalised personal possession since 1976, although cultivation of cannabis is still an illegal activity. In March 2018, Dutch ministers outlined plans to regulate the legal cultivation of cannabis in a pilot study of selected municipalities. In Spain, cannabis social clubs have existed since 2001. These allow for the collective cultivation and distribution of cannabis for registered members. As of July 2017, Catalonia legalised cultivation and consumption of cannabis. Both Germany and Greece recently voted for legalisation of medical cannabis.

1.1.1 Epidemiology of cannabis use

In 2015, the global number of users of cannabis was estimated at 183 million (UNODC 2017). In the most recent reports, amongst young people in the US and Europe, there is a stable level of cannabis use amongst 15-16 year old European and American students (EMCDDA 2017). In Europe, the prevalence of cannabis use amongst young people is lower than in the US (Fig 1.1). However, in the US, tobacco use is lower than cannabis use (Fig 1.1). Last year, prevalence reached 17.1 million in European young adults (15-16 years old) maintaining its role as the most commonly used recreational drug (EMCDDA, 2017).

In adults, cannabis use remains stable with 1% of European adults using cannabis daily (EMCDDA 2017). In the UK, 6.6% of adults aged 16-59 reported having smoked cannabis in the last year, along with 8% of pupils aged 11-15. Twenty-nine percent of adults in the UK have reported smoking cannabis at least once in their life (above the EU average of 26%) (NHS 2018).

The extent to which those millions of people are using tobacco with cannabis as their primary route of administration (ROA) was not evaluated in the EMCDDA European Drug Report 2017 apart from the following statement: “In Europe, for example, in contrast to the United States, cannabis is often smoked in combination with tobacco, and this is likely to have implications for public health policies”.

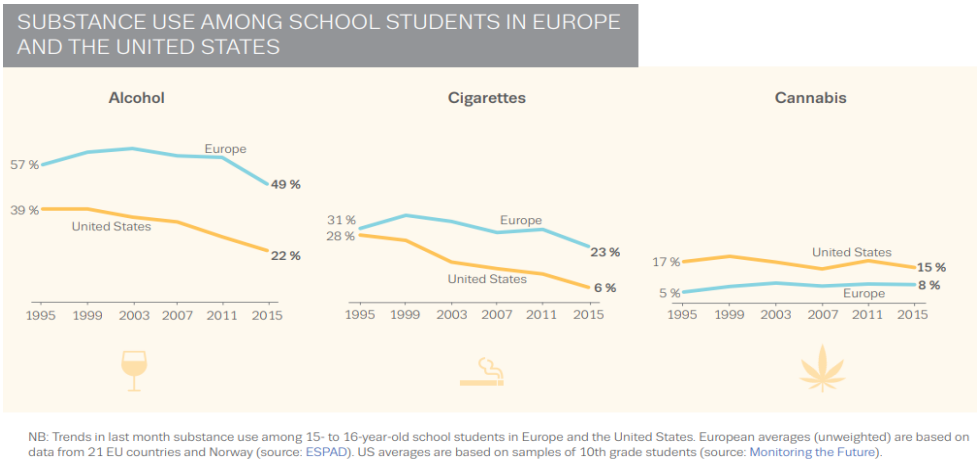


Figure 1.1. Rates of past month substance use among 15-16 years olds in nationally representative surveys of school students in Europe (ESPAD) and the US (Monitoring the Future).

1.1.2 Introduction to the Endocannabinoid System

The Cannabis Sativa plant can contain over 100 cannabinoids (Pertwee 2008) with different strains having different proportions of these cannabinoids. The two most studied exogenous cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Exogenous cannabinoids interact with the endocannabinoid system (eCB) (Devane et al. 1988) as well as with other target systems.

The eCB system is widespread throughout the body and brain and is thought to be a major homeostatic mechanism within the brain (de Fonseca et al., 2004). It regulates appetite, pain, ageing, learning, memory, depression and anxiety. The eCB system consists of (at least) two types of cannabinoid receptors, the cannabinoid receptor type 1 (CB1R) and the cannabinoid receptor type 2 (CB2R) and endogenous ligands that bind to these receptors, anandamide and 2-arachidonoylglycerol (2-AG). The CB1R are the most prevalent G-protein coupled receptor in the brain and plays many roles (Matsuda et al. 1990). Studies using radiolabelled full CB1 agonists show that most CB1Rs are based in the cerebellum. This is consistent with the potent effect of cannabis on movement (Kawamura et al. 2006). This is followed by the substantia nigra and globus pallidus where they are found mostly on GABAergic axon terminals that are projected from the striatum thus acting as homeostatic agents modulating inhibition. CB1Rs are also found in high density in the hippocampus, and in moderate concentrations in the neocortex, amygdala and hypothalamus, consistent with the actions of cannabis on memory, executive functioning, emotion, food intake and sleep. They are found in low concentrations in brainstem areas which control the respiratory and cardiovascular systems, consistent with evidence of no deaths attributable to overdose with cannabinoids (Herkenham et al. 1990). In the periphery, they are also found in the liver, thyroid, uterus, bones and testicles. CB2Rs are mostly found in the immune and gastrointestinal system (Pertwee 2008).

As well as the receptors, the eCB system also involves endogenous ligands or endocannabinoids, the two most researched of which are anandamide (Devane et al. 1992), and 2AG (Mechoulam et al. 1995). These are, unlike other neurotransmitters (e.g. serotonin, dopamine and acetylcholine), synthesised on demand and not stored within vesicles. They are produced from the *post*synaptic terminal, diffuse across the synaptic cleft and act on the CB receptors on the presynaptic terminal – a process known as retrograde signalling (see Fig 1.2). Thus, endocannabinoids act as a regulatory buffer and maintain homeostasis by preventing excessive neurotransmitter release (Bloomfield et al. 2016; Ruehle et al. 2012).

Finally, there are also enzymes that are involved in both the synthesis and catabolism of these endocannabinoids such as Fatty Acid Amide Hydrolase (FAAH), which degrades anandamide, and monoacylglycerol lipase (MAGL), which degrades 2AG. Once these endocannabinoids are released, their signalling is terminated quickly via cellular reuptake and hydrolysis enzymes.

THC, the primary psychoactive cannabinoid in cannabis, is a partial CB1 and CB2 receptor agonist (Pertwee 2008). CBD, on the other hand, has not had its precise mechanism of action fully elucidated. It has a low affinity to the CB1 and CB2 receptor (Bisogno et al. 2001; Jones et al. 2010) with recent research suggesting it is a negative allosteric modulator of the CB1R (Laprairie et al. 2015; Straiker et al. 2018). It is also an agonist at 5-HT1a receptors (Campos and Guimarães 2008; Zanelati et al. 2010), a TRPV1 agonist (Bisogno et al. 2001) and a partial agonist at dopamine D2 (high) receptors (Seeman 2016). It inhibits the metabolism and reuptake of anandamide by a process of FAAH inhibition (Bisogno et al. 2001; De Petrocellis et al. 2011).

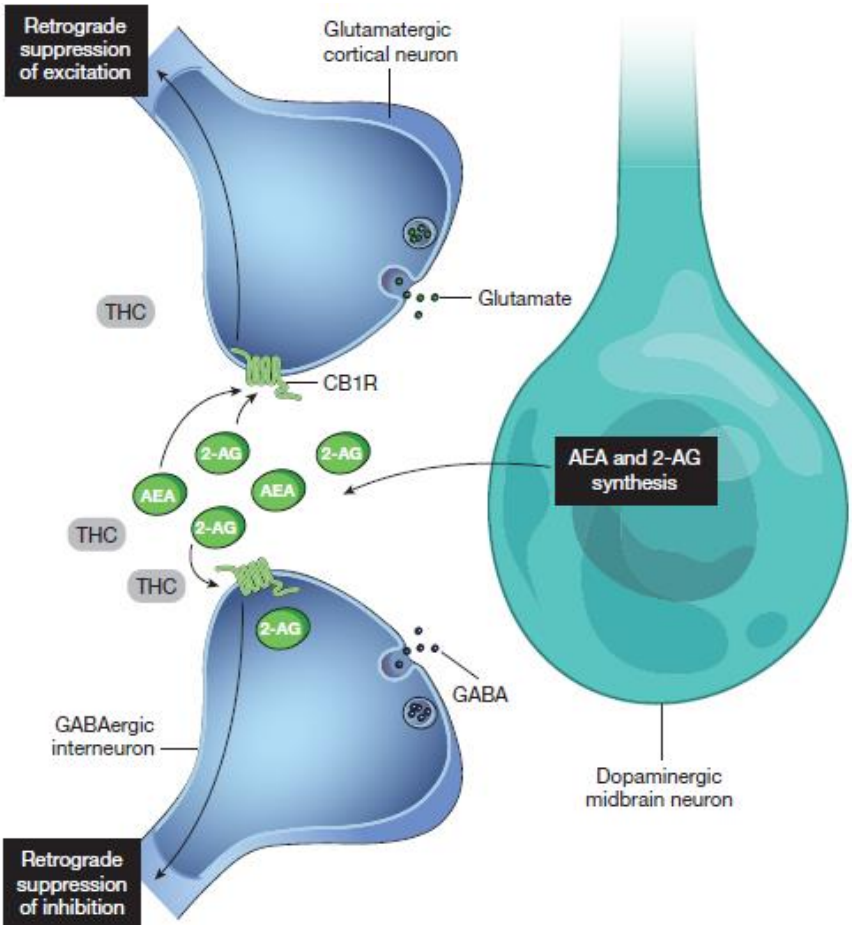


Figure 1.2. Reproduced from Bloomfield et al. (2016). Figure shows that THC binds to CB1 receptors on both glutamatergic (top left) and GABAergic (bottom left) neurons and therefore disrupts normal eCB retrograde signalling. Figure (right) depicts the eCB influence on dopaminergic midbrain neurons showing that "eCBs fine-tune the activity of the mesolimbic dopamine projections through the modulation of both excitatory and inhibitory signalling and THC disrupts this system."

1.1.3 Subjective effects of cannabis

Cannabis is most commonly consumed by smoking the dry flower, either with or without tobacco. The acute effects of cannabis have also been studied via smoked (combusted) vaporisation, oral and intravenous (IV) methods.

When cannabis is smoked, the acute effects of the drug are noticeable within minutes and these are mainly attributable to its primary psychoactive compound, THC. These effects include of an increased feeling of euphoria (also called being 'high' or 'stoned'), a reduction in alertness and the classic feelings of hunger (referred to as 'the munchies') (Crean et al. 2011). As well as these positive and desirable effects, negative effects such

as anxiety and acute psychotic-like symptoms can occur. Cognition and motor functions are also transiently disrupted. Therefore, people report difficulties in their abilities to plan and organise behaviours, remember information and control one's thoughts. These changes are dependent on dose (Curran et al. 2002b) and route of administration (ROA) (Newmeyer et al. 2017). For example, the peak effects occur within 30 minutes for inhaled and IV routes versus 1-2 hours for oral administration. They also vary according to an individual's cannabis use history i.e. tolerance effects (D'Souza et al. 2008), genetic makeup (Morgan et al. 2016a) and mental health factors. Some evidence suggests that effects are modified when combined of nicotine (Cooper and Haney 2009a; Penetar et al. 2005). However, whether the acute effects are modified by adding tobacco is currently unknown and a major focus of this thesis.

CBD generally occurs in much smaller concentrations than THC in recreational cannabis. It does not produce any intoxicating effects (Bhattacharyya et al. 2010; Haney et al. 2015; Hindocha et al. 2015a; Morgan et al. 2010b). It has properties that seem to be pharmacologically opposite of THC, even though its mechanism of action, is far broader. CBD has anxiolytic, antipsychotic, anti-epilepitoform and anti-seizure properties in humans (Bergamaschi et al. 2011; Crippa et al. 2011; Esposito et al. 2011; Iffland and Grotenhermen 2017; Jones et al. 2010). In preclinical models, it has been shown to have antioxidant, anti-inflammatory, neuroprotective and analgesic effects (Hampson et al. 1998; Maione et al. 2013). Importantly, CBD can partially offset some of the negative effects of THC on a range of tasks and measures including: paranoid symptoms, episodic memory, emotional processing, explicit liking and attentional bias to both drug and food images, and hippocampal integrity (hippocampal volume and *N*-acetylaspartate levels) (Englund et al. 2013; Hindocha et al. 2015a; Morgan et al. 2010a; Morgan et al. 2010b; Yucel et al. 2016).

1.1.4 Cannabis potency

The potency of both herbal and resin type cannabis is typically defined as the THC concentration, and this has been gradually increasing over the past 15 years (ElSohly et

al. 2016). Although the potency of cannabis is often defined as %THC alone, the acute and long term effects of cannabis are also likely to be influenced by concentrations of CBD. A recent report from the United States (US) suggests that the potency of US cannabis increased from 4% (1995) to 12% (2014) in just under 20 years (ElSohly et al. 2016). At the same time, the CBD content had fallen, thus the ratio of THC to CBD went from 14:1 to 80:1 in just under 20 years (1995-2014) (ElSohly et al. 2016). The increase in high potency cannabis varieties potentially poses a higher risk of dependence and psychosis (Curran et al. 2016; Di Forti et al. ; Freeman and Winstock 2015; Freeman et al. 2018). The same pattern of increased THC and decreased CBD content over the past 10 years has also been seen in the UK (Hardwick and King 2008; Potter et al. 2018), the Netherlands (Freeman et al. 2018; Niesink et al. 2015) and France (Dujourdy and Besacier 2017). “Skunk” or sinsemilla (indoor-grown seedless female flowering tops) is a colloquial term used to denote cannabis preparations high in THC, but also virtually void of CBD. This is in comparison to outdoor grown herbal cannabis, which tends to be less potent than “skunk”. These high potency varieties are the most available and accessible varieties in the UK (over 85% of police seizures; Potter et al. (2018)), and are basically the norm for cannabis users whatever their preference for less potent strains might be.

1.1.5 Acute effects of Cannabinoids on Memory

Frequent cannabis use has been associated with both acute and chronic effects on memory and learning. This is particularly important in regards to the developing brains of young people given the importance of the eCB system in brain development during puberty (reviewed in Curran et al. 2016). To summarize the effects on cognition, a recent systematic review suggested that verbal learning, memory and attention are the domains most consistently impaired and this can persist over time, post-intoxication (Broyd et al. 2016). The extent to which this impairment persists over time has been debated however, a meta-analysis of post-intoxication residual effects of cannabis found that impairments did not last longer than 25 days of abstinence (Schreiner and Dunn 2012).

Broyd et al. (2016) also found that a disconcerting number of studies do not report other substance use in their sample which included 33% of studies not reporting tobacco use. Effects on executive functioning and other neurocognitive domains may persist but the research is not clear yet. During acute intoxication, a series of neurochemical events take place in the mesolimbic system, which is depicted in Fig 1.3. In addition to this psychomotor function (i.e. movement, coordination, manipulation and motor speed) is severely impaired.

In this thesis, I will review the acute effects of cannabis, rather than the chronic effects. Furthermore, I will concentrate of two types of memory: verbal episodic and working memory.

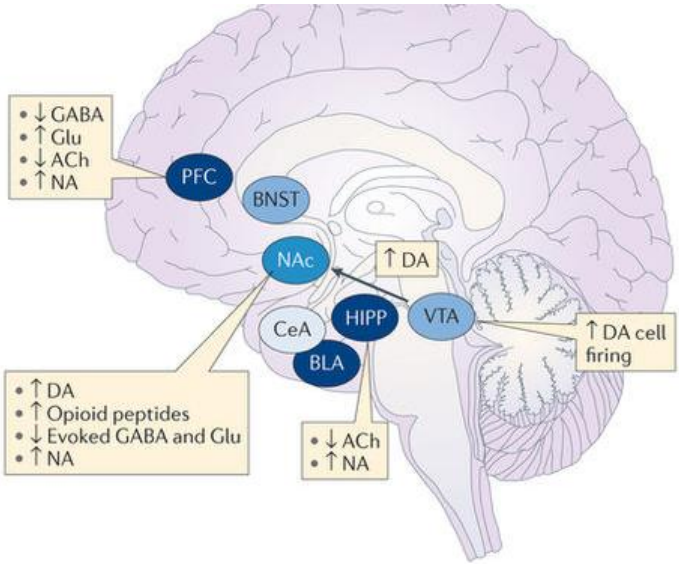


Figure 1.3. Reproduced from Curran et al. (2016). Acute THC induces neurochemical events in the mesolimbic system that are similar to those produced by other drugs of abuse, including increased dopamine release and an attenuation of evoked GABA and glutamate release in the nucleus accumbens. Disruptions in cognitive function (including attention and memory impairments) probably result from decreased acetylcholine release in the hippocampus and prefrontal cortex; reduced GABA release and increased glutamate release in the prefrontal cortex; and increased noradrenaline release in hippocampus and frontal cortical areas.

1.1.5.1 Verbal Memory

Verbal episodic memories are defined as personal contextualised autobiographic memory of past experience and it is distinct from semantic memory (defined as memory for factual information) although highly linked. One way in which this is operationalised is through a prose recall task. In this task, participants listens to a 30 second news clip and immediately recalls its contents. After 30 minutes, the participant is asked to recall the news clip again. It can also be assessed using a recognition memory task which involves recognition of a previously presented list of verbal stimuli - often used in place of a passage of prose - requiring less effort than a prose recall task. However, both tasks require some component of working memory.

Three processes are essential to a successful verbal episodic memory. Firstly encoding, which refers to the acquisition of new information. Secondly, the memory needs to be consolidated to protect against disruption and thirdly retrieval, the process of accessing

or recalling previously encoded memories. Verbal episodic memory deficits induced by THC/cannabis are unequivocal (Curran et al. 2002a; D'Souza et al. 2004; D'Souza et al. 2008). The hippocampus is dense in CB1 receptors and THC dose dependently impairs memory. THC has been shown to affect both immediate and delayed recall in infrequent users (Curran et al. 2002a; D'Souza et al. 2004; Hart et al. 2010). However, these studies do not specifically assess whether encoding, consolidation or retrieval are all affected.

In order to investigate the amnestic effects of cannabis, one can change the timing of drug administration relative to the phase of the task i.e. encoding, consolidation or retrieval. If immediate recall is intact after cannabis administration but delayed recall is impaired, this is suggestive of the drug affecting consolidation and/or retrieval rather than encoding. However, if both immediate and delayed recall are similarly affected, then this suggests the drug also effects encoding. It should be noted, that the processes are not fully dissociable in that encoding can provoke retrieval and retrieval can provoke encoding (Fletcher and Honey 2006).

Ranganathan et al. (2017) recently investigated the effects of THC on encoding and retrieval. In two experiments, participants were given THC either pre-encoding or post-encoding on the Rey Auditory Verbal Learning Test (Fig 1.4). Participants were unimpaired on both immediate and delayed recall when encoding occurred prior to THC administration. However, when encoding occurred after THC administration, both immediate and delayed recall were impaired. This supports the hypothesis that THC specifically impairs encoding. In this study, THC did not interfere with retrieval and the authors did not extend the findings to memory consolidation. This research is in line with fMRI research that suggests THC selectively effects encoding (during an associative memory task) (Bossong et al. 2012). It should be noted that this was a between-subjects design and a within subjects design (see chapter 3) would be stronger.

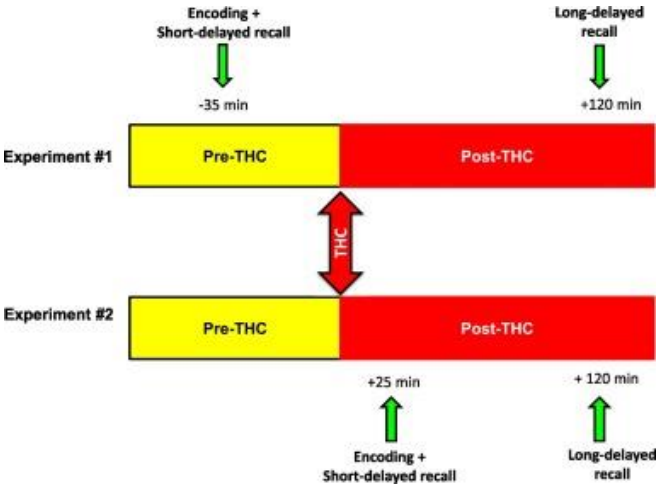


Figure 1.4. Experimental design from Ranganathan et al (2017). In experiment #1 (top panel) immediate recall was assessed prior to THC/placebo administration and delayed recall was assessed after THC/placebo administration. In experiment #2 (bottom panel) immediate as well as delayed recall were assessed only after THC/placebo administration.

There is some evidence that CBD protects against the negative effects of THC on verbal memory. For example, in a naturalistic study of cannabis users, Morgan et al. (2010b) found that those acutely using cannabis with a high CBD: THC ratio showed no impairment on both immediate and delayed prose recall compared to those who used who did not have detectable CBD in their cannabis. In another study that used hair samples to objectively assess THC:CBD levels. Those who tested positive for CBD, performed better on a recognition memory task, than those who tested negative for CBD (Morgan et al. 2012). These studies demonstrate the protective effects of CBD in street cannabis; however, the amount of CBD in street cannabis is decreasing (see section 1.1.4). A similar study, in controlled settings, where participants were pre-treated with oral CBD or placebo before IV THC. Results showed that the CBD pre-treated group performed better than the placebo group (Englund et al. 2013). Interestingly, this was not replicated in an acute study comparing the effects of vaporised THC 8mg, CBD 16mg and combined THC+CBD (Morgan et al. 2018a).

1.1.5.2 Working memory

Working memory is defined as the ability to hold and manipulate information (Baddeley and Hitch 1974) and is essential for everyday life, for example, it is correlated strongly with overall intelligence (Kyllonen and Christal 1990). Working memory can be measured by a multitude of different tasks. Classic working memory tasks include the N-back task and digit span tasks. Indeed many cognitive processes involve aspects of working memory such as learning, reasoning and comprehension (Baddeley 2010). The spatial N-back used in this thesis (Fig 1.5) presents participants with visual stimuli in a sequential order. The zero-back requires the participant to make a binary decision between when a set stimulus appears in a particular location around a central fixation cross (compared to when it does not). The zero back is a measure of vigilance or concentration. The one-back asks participants whether the present stimulus, is the same as the one seen previously. The two-back asks the whether the stimuli one sees is the same as one seen two stimuli previously. The dependent variables are often accuracy (% correct), reaction time, or the number of errors. Dependent variables can include maintenance (storage, rehearsal and matching) of information calculated as one-back minus zero-back. Additionally manipulation can be calculated as two-back minus one-back and reflects reordering and updating of information. Finally, signal detection analysis (Snodgrass and Corwin 1988) on performance on the N-back task can often be a more sensitive measure than basic indices. These indices include D Prime, a measure of discriminability (how well two stimuli can be distinguished) and Criterion, a measure of response bias.

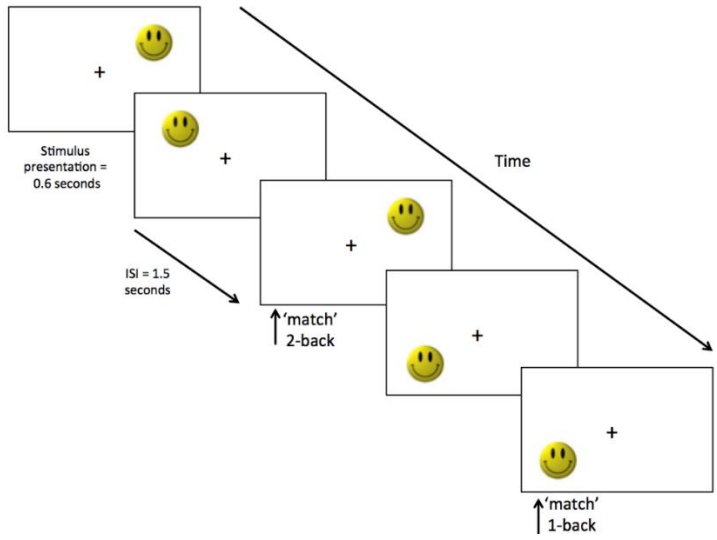


Figure 1.5. Spatial N-back Task. Participants are presented with a stream on stimuli in different locations, which they must monitor and respond accordingly with the instructions for each task type (0-back, 1-back, 2-back). A correct response for the 1-back task would be to respond that there were two stimuli in the same location chronologically.

Pharmacological challenge studies have shown that THC/cannabis impairs working memory (D'Souza et al. 2004; D'Souza et al. 2008; Hart et al. 2001; Morrison et al. 2009; Tinklenberg et al. 1970) but the effects are inconsistent depending on the tolerance of the sample (i.e. the history of cannabis use) and the ROA. Studies with infrequent and nondependent users remove these confounds of tolerance, recent use and residual effects and allows for the exploration of pure-drug effects.

In infrequent cannabis users, Curran et al. (2002a) used two oral doses - 7.5 and 15mg of THC and found no effects of two different types of task assessing working memory. D'Souza et al. (2004) also tested 22 infrequent users also using IV THC (0, 2.5 vs 5mg) and found that the number of correct responses on an n-back task was reduced but response time was not affected. Therefore, these two samples with similar levels of cannabis use show that the effects of IV/oral THC on working memory is not consistent for infrequent users. Results from studies of frequent users have also had mixed effects. These were dependent on the extent of cannabis use, ROA, sample size and task choice (Ilan et al. 2004; Kollins et al. 2015; Morrison et al. 2009; Vandrey et al. 2013).

CBD does not seem to protect against THC-induced impairment of working memory (Englund et al. 2013; Fadda et al. 2004). For example, CBD pre-treatment had no effect on working memory deficits induced by THC (Englund et al. 2013). Further, in yet unpublished research, Morgan et al. (2018b) compared 8mg THC, 16mg CBD and a combination 8+16mg THC and CBD vs. placebo, delivered via a volcano vaporiser. On an N-back task, Morgan et al. (2018b) found reduced sensitivity (d prime) for both THC and THC+CBD but no effect of CBD on its own.

1.1.6 Cannabinoids and psychosis

Cannabis smoking in people with psychosis occurs at a far higher rate than in the general population. Approximately 1 in 4 patients with schizophrenia smoke cannabis (Koskinen et al. 2010). Whether cannabis plays a causal role in psychosis is hotly debated and reviewed elsewhere (Gage et al. 2016; Ksir and Hart 2016; Moore et al. 2007; Myles et al. 2015; Radhakrishnan et al. 2015; Semple et al. 2005). Here I will very briefly summarise that literature.

Firstly, to clarify, psychotic symptoms, the two most prevalent of which are hallucinations and delusions, are key features of psychotic disorders. However, a psychotic disorder (e.g. schizophrenia, schizoaffective disorder, first episode psychosis (FEP), bipolar disorder or post-partum psychosis) is a diagnosed condition that is often persistent in one's life and is often accompanied by other symptoms such as deficits in memory and cognition. I will use the term 'psychotic-like symptoms' to define transient drug-induced psychotic experiences throughout this thesis.

The first study to assess the relationship between cannabis and psychosis was by Andréasson et al. (1987) who used military conscript registry data to analyse questionnaires from 45,570 Swedish men. The cannabis users were divided into frequent (+50 times ever) and infrequent users (less than 50). They found a dose response relationship - a threefold increase in risk in those who reported using cannabis more than 50 times by age 18. However, the problem with this classical study, and the many observational studies that followed it, is the assumption of causality (Gage et al.

2016). Furthermore Andréasson et al. (1987) specifically focussed on men. Case control studies where a cannabis user is matched to a control person, have also shown associations between cannabis and schizophrenia (Semple et al. 2005) but problems arise because the samples often do not match.

Meta-analyses of longitudinal cohort studies provide better evidence as they help summarize the literature. The first compared seven studies estimating that cannabis users experienced nearly three times the odds of having psychosis compared with non-users Odds Ratio (OR)= 2-9, 95% confidence interval (CI) 2.4–3.6 (Semple et al. 2005). Moore et al. (2007) analysed longitudinal population based studies and found that the OR was 1.41 (95% CI: 1.2-1.65) for individuals who had tried cannabis at least once in comparison to non-users. The most recent meta-analysis suggests the pooled OR is 1.46 (95% CI 1.24-1.72) (Gage et al. 2016). Marconi et al. (2016) found in the heaviest cannabis users, the OR for the risk of schizophrenia was 3.90 (95% CI: 2.84, 5.34), compared to non-users, suggestive of a dose-response relationship. Another recent and interesting finding from meta-analysis suggest that the time lag between initiation of regular cannabis and FEP was 6.3 years (Myles et al. 2015).

The type of cannabis is also implicated; using high potency street cannabis is considered higher risk than lower potency cannabis. Di Forti et al. (investigated 410 patients with FEP and 390 controls. Daily use of high potency cannabis was associated with a five times increase in the likelihood of suffering from a psychotic disorder. Use of hashish was not related to increased risk of developing psychosis. This may either be due to the protective nature of CBD in the hashish or because hashish is in general, lower in THC. However, this study was based on self-reported types of cannabis and no objective measure of cannabis was assessed e.g. urinary THC or cannabinoids in biological samples.

It should be noted that when adjustment for confounders occurs, the relationship between use of cannabis and the development of psychosis is often attenuated. One of the main confounders here is ‘other drug use’, especially tobacco use (See section 1.2.5

and 1.3.5). The main messages to take away from the epidemiological literature is that early onset and daily use of high potency cannabis lead to the greatest risk of developing psychosis (Di Forti et al.). However, the relationship between cannabis and psychosis may be (partly) bi-directional. For example, because cannabis use is not sufficient to cause psychosis on its own, so it may be that there is an underlying predisposition such as genetic liabilities, which are likely to mediate whether or not cannabis causes psychosis. In the case of the AKT1 genotype, two studies have found that variation in the AKT1 gene mediates psychotic like symptoms of smoked cannabis and increases the risk of developing a psychotic disorder in cannabis users in a case-control study design (Di Forti et al. 2012; Morgan et al. 2016b) Finally, although there is continued debate regarding causality, there is sufficient evidence to suggest that harm reduction strategies ought to be put into place for adolescent users of cannabis.

1.1.6.1 Acute studies of cannabis and psychosis

In randomised, double-blind placebo-controlled human laboratory studies, cannabis produces many symptoms that mimic psychosis, but are time-locked to the effects of the drug, allowing for further interpretation of causality. In these studies, both dose and route can be controlled. They also allow for the investigation of the individual and combined investigation of THC and CBD (Radhakrishnan et al. 2015). These studies have been conducted with IV, oral and vaporised THC as well as Nabilone and Marinol (Englund et al. 2017) and all reliably show that cannabis/THC increases psychotic-like symptoms, dose-dependently. The three clearest pharmacological challenge studies have been conducted with healthy controls (D'Souza et al. 2004) and more frequent users (D'Souza et al. 2008; Morrison et al. 2009). All three have shown that THC induced positive, negative and cognitive symptoms. D'Souza et al. (2005) conducted a unique study administering an acute THC dose to antipsychotic-treated patients with schizophrenia finding they were more sensitive to the negative effects of THC on memory but that both groups had similar THC induced psychotic symptoms positive and negative symptoms of cannabis.

Drugs that can block the acute effects of THC can potentially be used as treatments for psychosis as is the case with CBD (Iseger and Bossong 2015). In two studies, CBD has been shown to be a potent antipsychotic drug in people with a diagnosis of schizophrenia (Leweke et al. 2012; McGuire et al. 2018). In a double-blind, placebo-controlled, randomised, clinical trial of four weeks of CBD in comparison to amisulpride in people with schizophrenia, CBD performed equally well to the typical antipsychotic, however the side effect profile of CBD was much better (Leweke et al. 2012). Acutely, CBD does not produce any side effects except for slight sleepiness (Bergamaschi et al. 2011). A recent update on the side effects of CBD indicated that it has a favourable safety profile, which may help with patient compliance to the drug. However some important toxicological parameters have yet to be assessed (Iffland and Grotenhermen 2017).

In terms of *psychotic-like effects* in healthy individuals who smoke cannabis, Morgan and Curran (2008) found that those who were positive for THC only (in comparison to THC-CBD) experienced more psychotic like symptoms on the 'unusual experiences' subscale of the Oxford-Liverpool Inventory of Feelings and Experience (O-LIFE), a dimensional assessment of psychotic-like traits. This suggests that CBD may reduce the risk associated with cannabis use. This finding was replicated in a subsequent study in recreational but not daily users (Morgan et al. 2012). However, CBD did not affect psychotic-like symptoms when comparing cannabis users with high and low levels of CBD in their cannabis (Morgan et al. 2010b). CBD only effected psychotic-like symptoms in light cannabis users when given alone, but not when given in combination with THC in an acute pharmacological challenge study (Morgan et al. 2018b). Further research comparing the same dose of CBD, with and without THC are required to investigate the anxiolytic and antipsychotic properties of CBD.

The mechanism by which CBD is considered antipsychotic has also been explored. As previously noted, CBD is a FAAH inhibitor which means that it increases serum anandamide levels. Anandamide is reduced in those with FEP (Leweke 1999). This reduction can be reversed with typical antipsychotics (dopamine antagonists) suggesting

that anandamide is protective against psychosis via a homeostatic role of controlling excessive dopamine release (Leweke et al. 2015). Psychotic-like symptoms are related to levels of this endocannabinoid in the cerebrospinal fluid (CSF); a proxy measure for brain endocannabinoid levels. Anandamide levels are negatively correlated with the severity of psychotic symptoms and positively correlated with CBD-induced improvement in clinical presentation and anandamide levels in blood plasma (Giuffrida et al. 2004; Leweke et al. 2012). Finally, it has also been found that CSF levels of anandamide was reduced in frequent cannabis users, and these correlated negatively with psychotic-like symptoms in these individuals (Morgan et al. 2013b)

1.1.7 Cannabinoids and addiction

There are many definitions and conceptualisations of addiction (Sussman and Sussman 2011). One definition is 'a chronic condition involving a repeated powerful motivation to engage in a rewarding behaviour, acquired as a result of engaging in that behaviour that has significant potential for unintended harm.' (West and Brown 2013 page 18). In this thesis, I will be using addiction and dependence/use disorder interchangeably, because they are not distinct concepts.

Although much recent research has focussed on cannabis and psychosis, addiction is a more common problem. An estimated 1 in 11 may develop addiction to cannabis across their lifetime (Lopez-Quintero et al. 2011). The estimated chances of becoming dependent to cannabis after lifetime exposure (ever used) is 8.9% rising to 16% in those who start using in adolescence, which is considerably lower than for cocaine (20.9%), alcohol (22.7%) or tobacco (67.5%) (Lopez-Quintero et al. 2011). In the most recent US national data, 3 out of every 10 cannabis users developed Cannabis Use Disorder (CUD) (Hasin et al. 2015). Cannabis use is clearly a necessary condition for CUD, but since not all cannabis users develop CUD, its use alone is not sufficient for most cases. CUD is defined by the Diagnostic and Statistical Manual, Fifth Edition (DSM-5) as "a problematic pattern of cannabis use leading to clinically significant impairment of distress, as manifested by at least 2 of the symptoms occurring within a 12 month period" (APA

2013). Importantly, DSM-5 changes removed the DSM-IV legal problems criterion, and added criteria for craving and cannabis withdrawal. The symptoms of CUD include:

a) Cannabis is used for longer periods of time or in larger amounts than was intended
b) A persistent desire unsuccessful efforts to cut down or control use
c) A great deal of time is spent in activities necessary to obtain cannabis, use cannabis or recover from its effects
d) Craving, or a strong desire or urge to use cannabis
e) Recurrent use of the cannabis resulting in a failure to fulfil major role obligations at work, school or home
f) Continued use of cannabis despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use
g) Important social, occupational or recreational activities are given up or reduced because of cannabis.
h) Recurrent use of cannabis in situations in which it is physically hazardous
i) Use of cannabis continues despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis itself
j) Tolerance defined as: a) a need for markedly increased amounts of cannabis to achieve the desired effect b) a markedly diminished effect with continued use of the same amount of cannabis
k) Withdrawal, as manifested by either of the following: a) The characteristic withdrawal syndrome for cannabis b) cannabis is taken to relieve or avoid withdrawal symptoms.

Individuals who have experienced 2 or 3 symptoms are considered to have mild CUD. Moderate CUD is defined as 4 or 5 symptoms and severe as 6 or more.

Many individuals can use cannabis without incurring apparent harm. However, CUD prevalence rates, especially in American states where cannabis has become legal, for

medical or recreational use, is increasing (Hasin 2017; Hasin et al. 2015; Wen et al. 2015). This liberalisation may influence cannabis initiation, speed to transition to dependence, frequency and quantity of the drug used. Risk factors for CUD include the potency of the cannabis (Freeman and Winstock 2015; Freeman et al. 2018) as well as the co-morbid use of tobacco (Hindocha et al. 2015b), genetics and childhood trauma.

1.1.7.1 Cannabinoids and reward processing

There is mounting evidence that the eCB system is involved in motivation for rewards including the modulation of the rewarding effects of drugs (Lawn et al. 2016; Lupica et al. 2004; Martz et al. 2016; Parsons and Hurd 2015; Ruehle et al. 2012). The evidence for eCB involvement in pleasure, reward and reinforcement includes the fact that cannabis acutely causes euphoria – a pleasurable experience that users seek and a primary reason for use. Additionally, there is evidence to suggest that the eCB system modulates both dopaminergic and opioidergic signalling which are involved in reward processing (see Fig 1.2 and 1.3) (Hernandez and Cheer 2015). Self-administration paradigms are used to assess how reinforcing a drug is. While there is ample evidence that some humans self-administer cannabis, there has been mixed preclinical models – a measure of reinforcement (Justinova et al. 2005).

In humans there is mixed evidence whether THC administration leads to dopamine release in the striatum; research has shown both increased dopamine transmission (Bossong et al. 2009) and no difference in dopamine release following THC (Stokes et al. 2009). It should be noted that these studies used different methods of THC administration (vaporisation vs. oral, respectively) and ROA is important in determining the rewarding effects of a drug. When data from these two studies was combined, a small but significant (p=0.023) increase in dopamine release in the limbic striatum was found (Bossong et al. 2015). Given that some drugs of abuse increase dopamine release which is associated with drug-induced reward, these results suggest that THC shares a potentially addictive property with other drugs of abuse. Critically, addiction is not reducible to dopamine release a theory that has been heavily criticised and more relevant

to psychostimulant or alcohol abuse than drugs such as cannabis (Nutt et al. 2015). One of the major issues surrounding cannabis and reward processing is that cannabis is increasing in potency (see section 1.1.4). This suggests that high THC cannabis may increase the addictive potential of cannabis and potentially of other drugs. However, users are also titrating their dose, by adding less cannabis to joints (Freeman et al. 2014b) and inhaling less deeply so whether they are experiencing any increased reinforcing effect is debated.

Pre-synaptic CB1 receptors are critical in modifying signals along the mesocorticolimic dopaminergic pathway (see Fig 1.3) (Parsons and Hurd 2015). When THC or anandamide is administered, there is an increase dopamine in the Nucleus Accumbens (NAcc) (Oz et al. 2010; Solinas et al. 2006) leading to the rewarding effects in animals. Blocking the eCB system with rimonabant, a CB1 antagonist, reduces the rewarding effects of several drugs including THC and nicotine (Vries and Schoffelmeer 2005). At the same time, chronic cannabis users show a blunted response to the anticipation of reward in the striatum in fMRI research (Martz et al. 2016). van Hell et al. (2012) investigated the eCB system in reward processing in humans finding that THC challenge had no effect on reward responsivity but induced widespread attenuation of the BOLD respond to *feedback* of reward (but not neutral trials). This suggested that the eCB system is involved in the appreciation of natural rewards, relevant to addiction. Additionally, Jansma et al. (2013) compared healthy controls to those with nicotine dependence finding a reduction in the *anticipation* of reward in the striatum in those with nicotine dependence after THC challenge, in comparison to healthy controls. This study suggests that nicotine addiction is further associated with an altered eCB modulation of reward processing, and is important as it implicates the eCB system in reward processing.

1.1.7.2 Relative Reinforcing Efficacy as a measure of reward processing

The relative reinforcing efficacy (RRE) of a drug can be measured using hypothetical purchase tasks, which provide behavioural economic indices of the appeal of a

substance. In this thesis, I use the Marijuana Purchase Task (MPT) and the equivalent for tobacco - the Cigarette Purchase Task (CPT) (See section 1.2.5.1). Collins et al. (2014) investigated the RRE of cannabis in young heavy cannabis users who smoked on average 3 joints per day (without tobacco). The task required participants to say how many puffs of a joint of cannabis they would purchase at increasing prices from free ($0) onwards. They found that purchases became more elastic as price increased suggesting that people would buy less cannabis at higher prices. They were willing to buy cannabis until a single puff was equivalent to $38.07 when the average street price at the time of study was $7/joint (Collins et al. 2014). This research demonstrates how dependent cannabis users over-value the drug. When this study was replicated, it was found that those with at least one dependence symptom (in comparison to none) would purchase more cannabis when the drug was free and were more insensitive to price increases (Aston et al. 2015). Since the development of purchase tasks began with tobacco, the results were deemed similar to the tobacco results (MacKillop et al. 2012; MacKillop and Murphy 2013; MacKillop et al. 2008). However, these results have not been translated to UK participants where individuals smoke cannabis with tobacco and in these studies, researchers told participants that the cannabis was of high potency rather than typical cannabis or participant's normal cannabis that they smoke, which may have made the cannabis more appealing. Finally the acute effects of cannabis have not be assessed using the MPT. Overall, the RRE can be used as a measure of the demand of a drug.

1.1.7.3 Treatment of Cannabis Use Disorder

The number of first time treatment seekers for cannabis use problems has doubled in the past 10 years in Europe – suggesting CUD is becoming more of a problem for some people. Overall, the number of first-time treatment entrants for cannabis problems increased from 43 000 in 2006 to 76 000 in 2015 (EMCDDA 2017). In England and Wales, the number of under eighteens accessing specialist drug treatment with cannabis as their primary drug of dependence has increased by almost 50% in the last decade (9,000 in 2005 to 13,000 in 2014) (Brand et al. 2017) (depicted in Fig 1.6). Only a small

proportion of people will ever get help with their problems – this is partly because pharmacological treatments for CUD have not shown efficacy even after 20 years' worth of investigation (Sherman and McRae-Clark 2016).

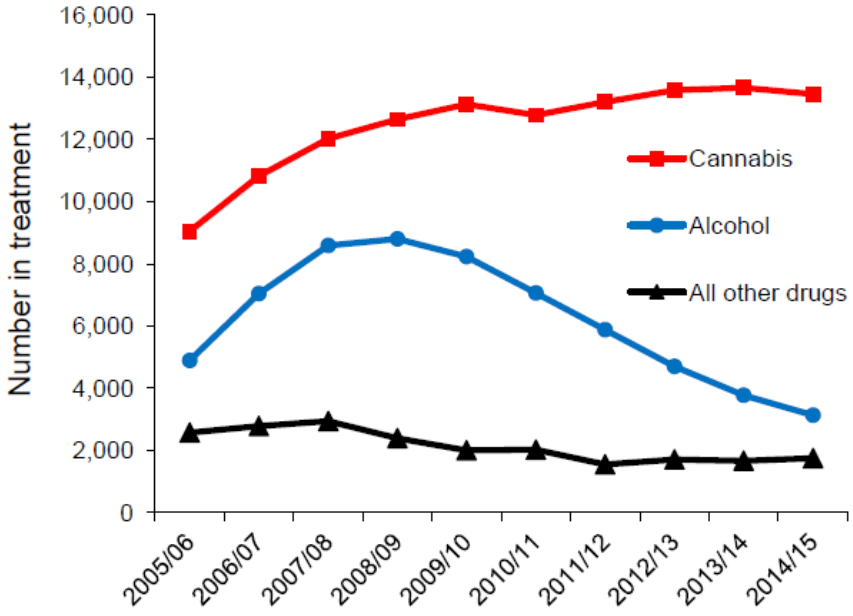


Figure 1.6. The number of under 18 year olds in specialist drug treatment in England, according to the primary drug of abuse – cannabis, alcohol or other that they receive treatment for (Data reproduced from Public Health England (NDTMS, 2014); Figure kindly provided by Dr. Tom P. Freeman.

1.2.7.3.1 Psychological treatments

A recent meta-analysis of RCTs for psychological therapies available for CUD assessed cognitive behavioural therapy (CBT), motivational enhancement therapy (MET), contingency management (CM) and relapse prevention (RP) (with a total of over 2000 participants) (Davis et al. 2015). Those who received psychological therapy fared better than 69% of those in control group (i.e. waiting list) but there was a lack of differentiation between treatments - suggesting any kind of psychological therapy can help with CUDs (Davis et al. 2015). In reality, CUDs seem difficult to treat with behavioural therapies which only give a 20% abstinence rate during the first 2 weeks of an intervention (Budney et al. 2007). Of those who achieve abstinence, 50% will relapse in a year (Budney et al.

2007) and there are usually large drop-out rates. Thus, one treatment that may be useful is a relapse prevention service aimed at increasing motivation to maintain abstinence and prevent relapse.

1.2.7.3.2 Pharmacological treatments

A variety of novel pharmacological treatments have been tested in clinical trials with varying degrees of success. Drugs that target the eCB system would be a logical strategy to treat CUDs because chronic cannabis use leads to CB1 downregulation (Hirvonen et al. 2012), which may be the source of withdrawal symptoms during a quit attempt as the brain returns to a state where cannabis is not regularly being administered. CB1 agonists therefore can reduce the withdrawal symptoms similar to Nicotine Replacement Therapy (NRT) for nicotine withdrawal. However, only moderate quality evidence has emerged for preparations containing THC compared to placebo according to a Cochrane Review (Marshall et al. 2014). Furthermore, there was very low quality evidence for antidepressant treatments, anticonvulsants, mood stabilisers and bupropion according to the strict Cochrane guidelines. Data on two treatments of gabapentin and N – acetyl cysteine were also insufficient. Overall, Cochrane suggests preparations containing THC had potential value but further research is needed (Marshall et al. 2014). A clear conclusion can be drawn from this analysis, which is that there has not been enough research on pharmacological treatments of CUD despite the clear population need.

Sativex (Nabixmols) which a 1:1 ratio of THC: CBD delivered as a buccal spray has been shown to reduce the severity and time course of cannabis withdrawal in comparison to placebo (Allsop et al. 2015). In another study, Sativex decreased craving and cannabis use but did not reduce withdrawal symptomology, however it should be noted that this study had a very high rate of payment for participants (855 Canadian Dollars) which may have led to an element of contingency management for abstinence (Trigo et al. 2018).

CBD alone may have potential as a novel treatment for CUD. In human experimental research, attentional bias (the ability of certain salient stimuli in the environment to “grab” attention more than other stimuli) to cannabis cues was lower in those who smoked

cannabis with higher levels of CBD versus low in CBD suggesting that CBD could protect against symptoms of addiction as such as attentional bias (Morgan et al. 2010a).

Attentional bias, as measured by dot-probe and Stroop tasks are important in-lab predictors of cannabis addiction as they are related to craving (Cousijn et al. 2013; Field et al. 2004; Vujanovic et al. 2016). Additionally, as reviewed above, CBD has properties that may make it ideal for drug cessation in that it is well tolerated (Bergamaschi et al. 2011; Iffland and Grotenhermen 2017), has no reinforcing effect in humans (Babalonis et al. 2016), does not alter the reinforcing properties of smoked cannabis (Haney et al. 2015), and is anxiolytic (Blessing et al. 2015; Campos and Guimarães 2008; Crippa et al. 2011). Its anxiolytic properties are particularly relevant as anxiety is a primary symptom of withdrawal. CBD is likely to be anxiolytic because it activates 5HT1a serotonergic receptors (Russo 2016; Russo et al. 2005).

Furthermore, animal research suggests CBD can reduce the ability of drug cues to cause relapse to heroin. Ren et al. (2009) showed CBD (5–20 mg/kg) attenuated cue-induced heroin-seeking behaviour and relapse, which was maintained for two weeks after CBD administration. Furthermore, human pilot research translated directly from Ren et al. (2009) showed a single dose of CBD can attenuate cue-induced craving in heroin users over a 24-hour period (Hurd et al. 2015). This supports one neuroimaging study which showed that relative to placebo, THC and CBD had opposite effects on activity of areas in the brain highly associated with salience attribution including the striatum, hippocampus and prefrontal cortex (Bhattacharyya et al. 2015), where THC increased, and CBD decreased activity. Taken together, the experimental evidence provides a strong rationale to hypothesise that CBD is a potential treatment for substance use disorders where the salience of drug cues may be key. CBD is now in Phase 2 clinical trials for the management of craving in people addicted to heroin. A phase 2 clinical trial for CUD, which tested 3 doses of CBD versus placebo and in combination with MET, which I contributed to prior to my PhD, has also recently been completed at the Clinical Psychopharmacology Unit at University College London.

1.2 Tobacco

Tobacco use is one of the largest public health threats according to the World Health Organisation (WHO 2015). The prevalence of cigarette smoking varies by country but approximately 1 in 5 adults smoke globally (Gowing et al. 2015). Half of these individuals meet the criteria for Tobacco Use Disorder (TUD) (Grant et al. 2004). It is estimated that tobacco use is the most preventable cause of mortality in the world. More than 7 million people each year die due to tobacco smoking. Less than 1 million of that is due to second hand smoke suggesting that most deaths are a direct result of smoking. Based on data from a 50-year observational study, smokers have their life expectancy shorted by 10 years, on average, compared to non-smokers (Doll et al. 2004).

In this thesis, I will be using tobacco, nicotine and smoking interchangeably for ease of writing but these terms are not interchangeable. Although nicotine is the primary component driving addiction, tobacco smoke also contains other psychoactive components such as Monoamine Oxidase Inhibitors (Lewis et al. 2007). However, it should certainly be acknowledged that nicotine itself is not necessarily harmful, but tobacco smoke is. Moreover, whereas the health benefits and harms of cannabis are debated, those of tobacco are not. As there have been numerous prior reviews of effects of tobacco use (Britton and Edwards 2008; Hatsukami et al. 2008; Jha and Peto 2014; Organization and Cancer 2004), this section will be substantially shorter than the previous section on cannabis.

1.2.1 Epidemiology of tobacco use

In the UK, during 2005-2006, smoking was estimated to cost the National Health Service (NHS) £5.2 billion (Allender et al. 2009) and in 2014-2015 there were 475,000 hospital admissions attributable to smoking (ONS 2016). As one of the world's most addictive drugs, about 69% of individuals who try tobacco will become addicted to it (Lopez-Quintero et al. 2011). Cigarette smoking in the western world is on the decline. In 2015, 17.2% of all people in the UK were smoking, less than 20.1% of adults who smoked in 2010 (ONS 2016). The average number of cigarettes smoked, by tobacco smokers; in

the UK is currently 11.3 cigarettes per day. Unfortunately, the prevalence of cigarette smoking is highest amongst young adults (25-34 years old). Individuals mostly start smoking in adolescence, before the age of 18 (ONS 2016). As can be seen in Fig 1.1 (section 1.1.1), cigarette smoking by both European and American school-aged children is rapidly decreasing.

Given the negative consequences of chronic tobacco smoking, it is unsurprising that around 70% of smokers in Great Britain want to quit (Lader and Meltzer 2003). In spite of this common desire, quit rates remain low and the chance of successful abstinence is poor (Schnoll and Lerman 2006). Novel treatments that target the different stages of addiction (intoxication, withdrawal, early abstinence and relapse) are therefore required to improve abstinence rates.

1.2.2 Introduction to the nicotine acetylcholine system

The nicotine acetylcholine receptors (nAChRs) are ubiquitous in the brain (Wu et al. 2006). Exogenous nicotine, the primary pharmacologically active substance in tobacco smoke, acts as an agonist at the receptor site and has a stimulating effect. At a cellular level, nicotine acts on the α4β2 subtype of nAChRs. The receptor consists of 5 subunits around a central water-filled pore that allows the passage of sodium, potassium and calcium when the endogenous ligand, acetylcholine, binds. nAChRs are also located in high densities in the thalamus, basal ganglia, frontal, cingulate and insular cortices (Clarke et al. 1984; Ding et al. 1996). The receptors are importantly located on the nerve terminals of DA neurones in the VTA, which projects into the NAcc. This leads to enhanced dopamine release, or in other words, nicotine is addictive because it highjacks neural circuitry that is essential for reward.

1.2.3 Subjective and cognitive effects of nicotine

Acute nicotine induces mild euphoria, enhances cognitive function and reduces stress and anxiety (Ernst et al. 2001; Levin et al. 2006; Warburton 1992) – effects that play a role in the initiation of smoking. The acute effects of nicotine are highly varied but some of the subjective effects include increased heart rate, reduced hunger, increased

attention and motor speed. This is dependent on the ROA, dose and individual differences such as smoking topography and nicotine metabolism. Nicotine is a cognitive enhancer and short term abstinence from smoking impairs cognitive function in multiple domains (Grabski et al. 2016). The deficits caused by abstinence can then be ameliorated by acute nicotine administration (Hughes 1992; Leventhal et al. 2010). In non-smokers, nicotine can have the opposite effect and be detrimental to cognition. Chronic smokers show poorer performance than non-smokers on verbal and visuospatial learning, visuospatial memory and processing speed as well as other cognitive domains suggesting that although nicotine is an acute cognitive enhancer, long term use is detrimental to cognition (Durazzo et al. 2012; Nooyens et al. 2008).

The acute effects of nicotine on cognition were reviewed by Heishman et al. (2010) who found the strongest effects of acute nicotine administration were on fine motor ability, attention accuracy and response time, short term episodic memory and working memory (with effects sizes ranged between 0.16 and 0.44 i.e. small to medium). In summarising the research on nicotine and cognition, it has been suggested that the strongest effects of nicotine are on tasks that require high attention, potentially because nicotine increases sensory gating abilities, thus allowing extraneous information to be filtered out, and therefore effects on memory is a consequence of this (Warburton 1992).

1.2.3.1 Cognitive effects of nicotine abstinence

Abstinence from tobacco causes a range of cognitive, affective and physiological effects in smokers and a Tobacco Withdrawal Syndrome has been defined in DSM-5 (APA 2013). The brain adapts to nicotine intake (Wang and Sun 2005), and therefore when nicotine is no longer available, re-adaptations occur which produce the withdrawal syndrome. Symptoms include difficulty concentrating, irritability, negative affect, insomnia, increased appetite and anxiety (DSM-5, APA). Anhedonia – the feeling of receiving little pleasure from life can also be a significant withdrawal symptom.

Grabski et al. (2016) reviewed the data on the effects of nicotine abstinence on three major categories of cognition: cognitive performance, attentional bias and impulsivity.

There was evidence that nicotine abstinence impaired performance on delay discounting (d=0.26; 95% CI: 0.07–0.45, *p*=0.005), response inhibition (d=0.48, 95% CI =0.26–0.70, *p*<0.001), mental arithmetic (d=0.38, 95%CI=0.06–0.70, *p*=0.018) and recognition memory (d=0.46, 95%CI=0.23–0.70, *p*<0.001). There was weaker evidence for the dot probe task, a measure of attentional bias (d=0.15, 95% CI= -0.01–0.32, *p*=0.072). There was no evidence for the Stroop (d= 0.17, 95% CI =-0.17–0.51, *p*=0.333) or smoking Stroop (d=0.03, 95% CI = -0.11–0.17, *p*=0.675).

Grabski et al. (2016) also reviewed the literature regarding the ability of these in-lab tasks to predict the success of smoking cessation success for at least one month. Thirteen studies were included. Tasks associated with cessation success at different timeframes included delay discounting, a discrete choice task, cue reactivity, continuous performance task, the Simon task and a startle response task. However, the data was too heterogeneous to conduct meta–analysis. Therefore, cognitive functioning during abstinence may predict cessation success, making early abstinence important target for treatment. Withdrawal is therefore a sensible target for medications aimed at helping people quit smoking.

1.2.4 Nicotine and Psychosis

As noted previously, the number of people who smoke in the UK is falling (Brown and West 2014). However this decline is not seen in people with mental illness (McManus et al. 2010; Szatkowski and McNeill 2014). In schizophrenia particularly, the prevalence of smoking was reported to be five times as high as other clinical and non-clinical populations (de Leon and Diaz 2005). These patients live for 14.5 years less than the general population; this risk is seen particularly due to cardiovascular risk as a function of smoking (Callaghan et al. 2014). The reasons why more people with psychosis smoke than the general population are less clear but smoking in schizophrenia is particularly hard to treat. There is certainly a need to identify novel treatments for people with tobacco use disorders and severe mental health disorders. Additionally, given that, cannabis models certain aspects of psychoses, and there are strong relationships

between cannabis and psychosis (section 1.1.6) and tobacco and psychosis, further investigation is required.

There are several hypotheses that attempt to account for why this comorbidity is so common. Firstly the self-medication hypothesis (Kumari and Postma 2005) posits that that smoking helps manage a pharmacological abnormality e.g. increasing dopamine that is caused by DA2 receptor antagonists (Goff et al. 1992; Smith et al. 2006) or purely increasing the metabolism of antipsychotic drugs (Desai et al. 2001) or indeed that it counteracts negative or cognitive symptoms of schizophrenia or potentially boredom and distress. This hypothesis has been heavily critiqued. Recently evidence suggests that chronic exposure to nicotine through cigarette smoking was not associated with cognitive functioning in individuals with psychosis, when controlling for premorbid IQ, age, gender and education (Hickling et al. 2018). Therefore, these findings do not support the self – medication hypothesis (Hickling et al. 2018).

A related hypothesis posits that the high prevalence of smoking in patients with psychosis is because of enhancement of the nAChR which leads to some beneficial effects in schizophrenia, including improving sensory gating deficits (Adler et al. 1993), pre-pulse inhibition (Hong et al. 2008; Kumari et al. 2001) and some types of cognition (Dépatie et al. 2002; Levin et al. 2006). The reason nicotine may help with these is because smokers with schizophrenia show lower B2 nAChR subtype availability compared to smokers (D'Souza et al. 2012b).

Additionally, Chambers et al. (2001) posit that there is a single neurobiological abnormality that gives risk to both addiction and psychosis, independently. These include abnormalities in hippocampal formation and the frontal cortex. In this explanation, addiction to tobacco and psychosis are correlated, but not causally related to each other.

More recently, epidemiological evidence suggests that this relationship could be operating in the opposite direction. Gurillo et al. (2015) conducted a recent meta-analysis investigating 61 studies of almost 15000 smokers. Smoking prevalence amongst patients was 57% and the overall risk of smoking in individuals with FEP was 3 times

higher in comparison to non-smokers. This research suggests that tobacco may have a causal role in psychosis and is consistent across populations. Furthermore, plausible mechanisms between the nicotine and dopamine systems were suggested. However, this study did not address any potential confounding. Kendler et al. (2015) utilised the Swedish Registry data and found that both light and heavy smoking was associated with the increased risk for schizophrenia suggesting the relationship was dose dependent (Kendler et al. 2015). However, after adjustment for socioeconomic status, other drug use and family history of psychiatric disorders, the relationship was attenuated.

In conclusion, smoking *may* help modulate the symptoms of psychosis and it may also be causal in the development of psychosis (however, as previously mentioned in section 1.1.6 - causation is a tricky issue). Regardless, if tobacco use is disproportionally high amongst those with schizophrenia, and the evidence suggest this *may be* causal, then it is certainly time to create a public health response for this left-behind population.

1.2.5 Nicotine addiction

The mesocorticolimbic dopamine system is particularly important for nicotine addiction. Acting mainly at the midbrain nAchRs, nicotine increases the firing rate of these dopamine neurones thus increasing the amount of dopamine in areas such as the prefrontal cortex and NAcc (De Biasi and Dani 2011).

The incentive sensitisation theory of drug addiction proposed by Robinson and Berridge (2001) suggests that repeated self-administration of an addictive drug like nicotine, leads to an association between that drug and reward. This increases the motivational significance (i.e. “wanting”) of that drug and cues associated with that drug. Drug addiction is therefore characterised by increased “wanting” - which is the primary driver of addiction (Berridge 2012; Tibboel et al. 2015) and potentially reduced anticipated pleasure or “liking”.

One way to index this “implicit wanting” is through an individual’s attentional bias to drug cues (Tibboel et al. 2015) as I discussed in section 1.1.7.3.2 in regards to cannabis use. Attentional bias to *cigarette* cues predicts short-term relapse (Waters et al. 2003) and is

thought to play a causal role in maintaining tobacco addiction (Franken 2003). Attentional bias at a short (compared to longer) exposure interval is particularly important as tobacco abstainers show greater bias to drug cues only implicitly as seen in the very short stimulus exposure (Freeman et al. 2012a).

1.2.5.1 Tobacco and reward processing

Dependence on a drug like nicotine can also be characterised as a hypersensitivity to drug rewards (Robinson and Berridge 2001) and hyposensitivity to non-drug rewards (Goldstein and Volkow 2002; Koob and Le Moal 2008; Lawn et al. 2015). As discussed in section 1.1.7.2, the demand for drugs (drug reward), relative to money (non-drug reward), can be measured by purchase tasks such as the CPT or the MPT (MacKillop et al. 2008). These give a real-world indication of the value of drugs for that individual (Bickel et al. 2014b) and most likely capture aspects of explicit motivation or "wanting". Performance on the cigarette purchase task (CPT) has been associated with nicotine dependence, daily smoking and objective measures such as CO levels (Mackillop et al. 2016; MacKillop et al. 2008).

The hedonistic aspects of drug addiction (i.e. drug "liking") have been far less investigated than the compulsive aspects (drug "wanting"). Drug "liking" is a subjective and affective response that can be measured by Pleasantness Rating Tasks in humans and is often assessed by taste reactivity in rats (di Pellegrino et al. 2011).

1.2.5.2 Tobacco use disorder treatments

Diagnosis of TUD occurs with the Fagerstrom Test of Nicotine Dependence (FTND) or with DSM-5-TUD criteria. There are many treatment aids for dependent tobacco smokers, which can be broadly divided into nicotine and non-nicotine treatments.

First line pharmacological treatments include NRT, which has the primary role of minimising withdrawal symptomology. There are many ROAs of nicotine, which include gum, patch, inhalers and lozenges. NRT are based on the principal that nicotine delivered via a variety of routes can replace some of the effects of cigarettes, so therefore

reducing addictive potential. It has been hypothesised NRT can desensitise brain nicotinic receptors thus leading to reduced reinforcement from cigarettes (Benowitz et al. 1997).

Research from the Cochrane Library suggests that NRT increases the rate of quitting by 50-70% compared to placebo or non-NRT control group (Stead et al. 2008). However, after the first year, about 30% relapse within one or two years, suggesting the long-term benefit of NRT is modest (Etter and Stapleton 2006). Some suggest that the effectiveness of NRT no longer remains significant after controlling for multiple sources of bias (Stanley and Massey 2016).

Non-nicotine medications include Bupropion Sustained-Release, which is a noradrenaline-dopamine disinhibitor. Bupropion works by blocking the reuptake of dopamine and noradrenaline thereby increasing their levels in the synapse. Therefore it is considered a non-competitive antagonist of the nAchR. Bupropion is also a first line therapy used in the UK and is equivalent to NRT in regards to quitting success (Cahill et al. 2016).

Varenicline on the other hand is a nAchR α4β2 partial agonist and provides relief from withdrawal by blocking the reinforcing effect of nicotine (Jorenby et al. 2006). In meta-analyses, varenicline is more effective than placebo however there was equivalent efficacy between bupropion and NRT (Cahill et al. 2016). Varenicline proved better than bupropion and single NRT, but not combination NRT. The gold standard is a pharmacological agent (e.g. varenicline), with NRT and counselling (Stead et al. 2016; Stead et al. 2008)

Medications targeting addiction often target the withdrawal syndrome. The problem with both nicotine and non-nicotine medications is that they come with certain side effects. For NRT, this is dependent on the type of product and can range from skin irritation, for patches, to gum and mouth irritation for nicotine gum and tablets. For non-nicotine medications, side effects include nausea/vomiting, sleep disorders, flatulence, dry

mouth, insomnia, heartburn and dyspepsia which effect 20%-40% of quitters (Cahill et al. 2016; Hatsukami et al. 2008).

1.2.5.3 Endocannabinoid involvement in nicotine addiction

There is a high likelihood that the eCB system is involved in nicotine addiction (Gamaleddin et al. 2015; Parsons and Hurd 2015; Robinson et al. 2017; Scherma et al. 2016; Serrano and Parsons 2011). There is a close overlap in cannabinoid and nAChRs in certain brain areas, which are involved in addiction, including the midbrain, but also the hippocampus and amygdala which are involved in drug related memory and emotion (Le Foll and Goldberg 2005; Picciotto et al. 2000).

Modulation of the eCB system, either pharmacologically or genetically, by changing CB1 receptor activity, changes reward-related behaviour in pre-clinical models. This has been shown in rodents in regards to alcohol, opiates, amphetamines (Serrano and Parsons 2011). In relation to nicotine dependence, THC and other CB1 agonists such as Win 55-212, increases nicotine conditioned place preference (CPP), a measure of the motivational effects of a drug (Valjent et al. 2002), nicotine self-administration (Gamaleddin et al. 2012) and reduces withdrawal in rats (Balerio et al. 2004). In CB1 knock out mice, CB1R agonists are no longer able to produce nicotine CPP. Moreover, antagonists of the CB1 receptor (e.g. rimonabant) decreases nicotine CPP (Forget et al. 2005; Le Foll and Goldberg 2004) decreases self-administration as well as the cognitive effects associated with nicotine withdrawal in a rat model (Saravia et al. 2016).

In human studies, rimonabant has been shown to decrease relapse to smoking (Cahill and Ussher 2011). Indeed, in clinical trials of rimonabant, it was shown to increase rates of abstinence by 1.5 times (Robinson et al. 2017). Although potentially effective, rimonabant was withdrawn from the market in 2008 due to potentially serious side effects, which included suicidality. Since rimonabant, drugs that effect the eCB system for nicotine addiction have been minimally investigated. Overall research suggests that the CB1R is essential for nicotine reward.

1.2.5.4 Cannabidiol in the treatment of tobacco use disorders

As I mentioned in section 1.1.7.3, CBD demonstrates some properties that might make it a potential pharmacotherapy for addiction. It may be a particularly suitable drug for smoking cessation include its lack of subjective effects (Hindocha et al. 2015a) it is anxiolytic (Bergamaschi et al. 2011; Fusar-Poli et al. 2009) and antipsychotic (Leweke et al. 2012; Leweke et al. 2015; Schubart et al. 2014) properties in humans. There is also evidence that CBD also blocks impairments induced by THC (see section 1.1.5).

The first human pilot study to investigate CBD as a treatment for nicotine dependence randomised 24 participants to either one-week of CBD inhaler (400 µg per depression with ~65% bioavailability) or placebo inhaler. Participants were instructed to use the inhaler when they had the urge to smoke. Results showed that CBD reduced the number of cigarettes smoked by almost 40% and there was some evidence that this was maintained in the 2 week follow up (Morgan et al. 2013a). A recent *in vitro* study suggested that CBD could also inhibit the function of nAchRs (Mahgoub et al. 2013).

Thus, there are several potential mechanisms by which CBD may be a useful treatment for TUD, but human laboratory and clinical data are needed. Follow-up research regarding the mechanism that might lead to reduced cigarette consumption has not been investigated.

1.3 Cannabis and tobacco co-use

Comorbid addictive disorders have a hidden mortality and morbidity and our ability to treat them is very limited. Interactions between NaChRs and the eCB system may underlie the widespread practise of cannabis and tobacco co-use. Chapters 2-5 of this thesis therefore aims to elucidate the extent to which these two drugs are used together and the psychopharmacology of combined cannabis and tobacco use.

Firstly, a note on terminology. There has been no consensus on the correct terminology in this area and therefore different authors are using different terminology to refer to the same concept. Additionally, sometimes authors are not clear on their own terminology, and when that is the case, I will use their terminology and not my own.

I use the term co-use as an umbrella term to refer to the use of both cannabis and tobacco. Concurrent use is defined as the use of both substances individually e.g. smoking cannabis and smoking cigarettes. I also use the term combined use to describe the use of cannabis and tobacco in a single product, such as a joint or spliff (cannabis and tobacco combined together in rolling paper and smoked) or blunt (hollowed out cigar filled with cannabis). This is sometimes called "mulling" in the literature but not a term regularly used anymore. Most of the US-based epidemiological research measures *concurrent use* but sometimes account for combined use through the use of blunts, whilst negating other ROAs. Therefore, I will use co-use more often than concurrent use, in order to have complete accuracy. I have also utilised the terms "Tobacco ROA" vs "Non-Tobacco ROA" in chapter 2. This is because the same route can be used with and without tobacco e.g. a pipe. Further, it is the terminology of the Global Drug Survey.

1.3.1 Epidemiology of cannabis and tobacco use

When considering cannabis and tobacco co-use, the most commonly cited data comes from Peters et al. (2012) who suggests that "between 41% and 94% of adult cannabis users, and half of adult cannabis treatment seekers, smoke tobacco". Equally, "cannabis use amongst tobacco users is between 25% and 52%, with at least 29% using cannabis weekly" (Peters et al. 2012). However, these data were derived over 10 years ago, and were limited to the United States (US).

Tobacco use rates are high amongst cannabis users; Schauer et al. (2016) found that 68.6% of those who had used cannabis in the past month, had also used tobacco in the past month. This increased to 78.3% if the use of blunts (a form of combined use) was included in the analysis. Hasin et al. (2016) used representative epidemiological data from the National Epidemiologic Survey on Alcohol and Related Conditions–III to show that 12-month CUD was associated with 12-month TUD and that this association became stronger across increasing CUD severity. The odds ratio for mild CUD was 4.8 (CI: 3.86-5.97); for moderate CUD was 7.3 (CI:5.11-10.41) and for severe CUD was 10.5 (CI 7.35, 15.05).

Cannabis use rates are also high amongst tobacco smokers. Data from the US National Survey on Drug Use and Health (NSDUH), which is a nationally representative household survey, suggests 18% percent of those who had used tobacco in the past month, reportedly used cannabis in the past month, between 2003-2012 (Schauer et al. 2016). Furthermore, 50% of young people (18-24) smoking cigars in the US, reported current cannabis use (data collected in 2013-2014) (Strong et al. 2018).

Between 2003 and 2012 co-use increased from 4.4% to 5.2% (Schauer et al. 2016). Co-use was always higher amongst those 18-25 in comparison to older ages (Degenhardt et al. 2013). The odds of co-use are greatest amongst young males, those with poorer health, binging or heavy drinkers, and those who had other past month substance use (Ramo et al. 2012). Co-users also had a lower likelihood of planning to quit tobacco for good (OR = 0.75, 95% CI 0.58, 0.98) (Ramo et al. 2012).

Goodwin et al. (2017) analysed data from the NSDUH which assessed 725 010 individuals aged 12 or over between 2002 to 2014. This study showed that daily cannabis use occurs (almost) exclusively among both non-daily and daily tobacco smokers, when compared to former and never cigarette smokers. Furthermore, daily cannabis use has increased in tobacco smokers between 2002 and-2014 from 0.98% to 2.79% in a linear fashion. However, daily cannabis use increased most rapidly amongst former cigarette smokers which may suggest some level of substitution (Goodwin et al. 2017). This data does not account for American states where medical marijuana was legal. In these states, cannabis use has a higher prevalence than states without medical marijuana, which may in turn affect cigarette use, nicotine dependence and co-use. Indeed, preliminary data suggests a higher proportion of past 30 day cigarette and cannabis co-users resided in states where medical marijuana was legal than where it was illegal (5.8 vs. 4.8%) (Wang et al. 2016).

Moreover, the issue of co-use seems to be gaining some traction as very recent research from the NSDUH now suggests that co-use is more prevalent that cannabis alone or tobacco alone use among US youth aged between 12-17. Most of this co-use was

because of the use of blunts with 8.5 in every 10 young American co-users reporting the use of blunts (Schauer and Peters 2018). Co-use was associated with higher prevalence of past year cannabis dependence, when compared to cannabis-alone users and higher past-month risky alcohol and other illicit drug use (when compared to tobacco-alone and cannabis alone user groups). These constantly changing epidemiological trends suggest that ongoing research and monitoring is required for our understanding of co-use behaviour amongst young people.

1.3.2 Concurrent versus combined use

Much of the research investigating cannabis and tobacco use suffers from being unable to detangle the association of cannabis *with* tobacco (combined use; for example in joints or blunts) and using cannabis *and* tobacco (concurrent use; cannabis smoking and cigarette smoking separately) and there is a paucity of data available to solve this. The distinction becomes important as those using cannabis *with* tobacco (combined use) seem to have higher rates of DSM-IV cannabis abuse, even when adjusting for cannabis use and cigarettes smoked (Agrawal et al., 2009). Agrawal et al. (2009) found those who used smoked tobacco, in comparison to smokeless forms, were 3.3-4.5 times more likely to develop cannabis dependence (even after co-variate adjustment, and in over 43 000 US adults). This may represent either a physiological adaption to 'smoking', may be related to cultural or social factors surrounding ROAs (Agrawal and Lynskey, 2009) or related to residual confounding (Section 1.3.3.4). Combined use represents a specific potential for nicotine exposure, making users more likely to develop nicotine addiction but also compounded health effects. Indeed, a recent systematic review suggests that combined cannabis and tobacco use was associated with indicators of problematic use, including reduced perception of risk and increased likelihood of dependence (Schauer et al. 2017). As discussed above, young co-users in a representative US survey show greater dependence symptoms than cannabis alone users (Schauer and Peters 2018).

The ability to make conclusions about the health outcomes of co-use is further hindered by the wide variations of designs used. Schauer et al. (2017) conducted a systematic

review, which found only 4 experimental studies that investigated when cannabis and tobacco were combined. Forty-five studies were identified, most of which were descriptive or observational in nature, 10 were qualitative, 3 used mixed methods, and 5 used a causal research design, of which 4 were experimental and 1 was quasi-experimental.

Of the 5 causal designs, only one directly compared the effects of cannabis alone versus co-use in 24 blunt smokers using a within-subjects, randomised, double blind, and placebo-controlled study. They compared the subjective, physiological and pharmacokinetic effects of cannabis, smoked in two ways, via blunts (hollowed-out cigar filled with cannabis; therefore exposing participants to tobacco) and joints without tobacco (specifically defined as cannabis alone within rolling paper). They found that "joints without tobacco" produced greater plasma THC, subjective, strength ratings and quality effects compared to blunts, and the effects were greater in women than in men. Blunts (cannabis with tobacco) were equivalent to these "joints without tobacco" in heart rate and CO, despite lower plasma THC levels. However, the explanation for lower THC levels with blunts is likely due to a procedural flaw in which blunts and joints were held in cigarette holders, but due to the cigar shell being thicker, it was more difficult to inhale.

The next three studies administered cannabis and tobacco in joints but kept the amount of tobacco static and varied the % of THC. Therefore, these studies cannot specifically speak to cannabis and tobacco combined use (Hunault et al. 2009; Hunault et al. 2008; Hunault et al. 2015). The final study from Moolchan et al. (2005) examined how blunt use influenced the likelihood of having a positive CO testing. In 37 adolescents, the use of blunts was associated with a greater level of positive CO (>8), compared to non-blunt users (Moolchan et al. 2005).

Despite extensive literature searches and as far as I am aware, there have been no experimental studies that have investigated the cognitive and psychological effects of cannabis and tobacco via combined administration.

1.3.3 Mechanisms underpinning co-use

The mechanism by which these drugs relate to each other and to dependence likely varies by individual experiences, and for cannabis and tobacco specifically, is likely goes beyond mechanisms that relate other polysubstance use (Connor et al. 2014). It is also the case that the importance of each of these mechanisms may vary by stage of addiction or drug use career (Hines et al. 2016).

1.3.3.1 Gateway hypothesis

A gateway drug is defined by three factors which relate to the temporal sequence of initiation: Sequence, Association, and Causation (Agrawal et al. 2012). The gateway hypothesis posits that there is causal sequence in the use of psychoactive substances that go from “softer” drugs to “harder drugs” (Kandel 1975). Cigarette smoking therefore is considered a gateway to “harder drugs” such as cannabis.

There is evidence to suggest that the gateway from cigarette smoking to other drug use is realistic even though this particular hypothesis has received a lot of criticism. Kandel (1975) reported data from over 5000 students showing transitions from ‘no drug use’ to ‘licit drug use’ and then cannabis and or other illicit drugs. They conclude that those who begin smoking cigarettes or drinking alcohol at an early age are more likely to be a regular cannabis user in the future (Ellickson et al. 1992; Kandel et al. 2006; Mayet et al. 2016; Yu and Williford 1992). However, as suggested previously, there is confounding by unaccounted factors, such as conduct problems and other internalising/externalising problems, which may pre-dispose individuals to drug use (Degenhardt et al. 2009; Korhonen et al. 2010). Furthermore, research suggests that the order of initiation, which is fundamental in the “sequence”, does not play a role in subsequent substance use disorder aetiology/development (Patton et al. 2005; Tarter et al. 2012). From what is know about the relative harms to users and society, and overall population health burden from cannabis in comparison to tobacco. Thus, the gateway hypothesis is considered an outdated viewpoint (Nutt et al. 2010; Whiteford et al. 2013).

1.3.3.2 Reverse gateway

One of the major challenges to the gateway hypothesis is that there are violations to the sequence of use. One of these is the reverse gateway hypothesis which suggests that the use of cannabis can come before the use of tobacco (Patton et al. 2005). This may be due to the higher taxation and control policies related to tobacco whist cannabis remained on the black market i.e. easy to acquire. The reverse gateway theory has been specifically applied to the relationship between cannabis and tobacco, and is not a theory that can be generalised to other drugs. This is largely because the reverse gateway hypothesis assumes the shared ROA (see section 1.3.3.4). It is clear from the epidemiology of co-use that there is a bidirectional relationship between the two drugs (Badiani et al. 2015).

1.3.3.3 Common liability model/ addiction vulnerability hypothesis

An alternative hypothesis to the gateway hypothesis is the “common liability model”. This model posits non-specific liability to all drug addictions regardless of the specific substance. For advocates of this model, the idea of sequenced drug use is a function of chance and they suggest that because the gateway hypothesis is chronological, it makes an assumption that cannot necessarily be tested.

The common liability model is derived from the high genetic correlations between liabilities to different drug addictions determined by twin and other genetic studies (Van Leeuwen et al. 2011; Vanyukov et al. 2009). Indeed, there is evidence of a genetic relationship to the liability to use cannabis and tobacco (Agrawal et al. 2010; Kendler et al. 2008). Additionally there are shared environmental influences e.g. peer influence (Agrawal et al. 2012).

Non-drug specific mechanisms e.g. generalised reinforcement learning, impulsivity, reward preference, incentive motivation, and stress responses, make individuals liable to both drug abuse and other behavioural problems (Vanyukov et al. 2012). As evidence of this, Grucza et al. (2017) who recently investigated this utilising 12-17 year old from the NSDUH with trend analysis showing a net *decline* in substance use delinquent

behaviour over 12 years which suggesting a single underlying trend connecting drug use and other behaviours.

1.3.3.4 Route of administration (ROA)

ROAs, and especially inhalation ROAs, are important because the aero-respiratory alterations produced by smoking (e.g. cigarettes), may enable processes in favour of (e.g. cannabis) inhalation (Agrawal and Lynskey, 2009). ROAs can alter the onset, intensity and duration of the subjective experience of the drug as well as the addictive potential and consequences of use. Use of tobacco (e.g. in joints) may confer a 'practical advantage' to cannabis users, in as much as tobacco can increase the amount of delta-9-tetrahydrocannabinol (THC) inhaled per gram by up to 45% (Van der Kooy et al., 2009). Preclinical research suggests tobacco pre-treatment may increase the reinforcing properties of THC (Solinas et al., 2007). Practically, smoking cannabis with inexpensive tobacco is economically advantageous as it dilutes the cost of the more expensive cannabis. Therefore, ROAs may play a large role in the use of both drugs. However, not all studies agree that tobacco enhances the reinforcing effects of cannabis (Haney et al. 2013). The implications of the ROA hypothesis, are that those who use both are more likely to develop respiratory distress than cannabis, or tobacco, only users (Agrawal et al. 2012; Agrawal et al. 2009). With the proliferation of cannabis, there has been a huge diversification of routes of administration, and whilst the classical view is that cannabis is smoked via a joint, this seems to be changing with new routes, such as dabbing~~,~~ developing prevalence

1.3.4 Cognitive effects of co use

It has been hypothesized that tobacco compensates for adverse cognitive and affective consequences of cannabis (Rabin and George, 2015; Schuster et al., 2016). This hypothesis posits that cannabis and tobacco have synergistic effects. In regards to cognition, this introduction has shown that cannabis and tobacco have opposite effects on aspects of cognition (see sections 1.1.5 and 1.2.4).

Individuals smoking cannabis and cigarettes have less episodic memory impairment when drug free compared to cannabis users alone (Schuster et al. 2015), but experience worse cognitive withdrawal symptoms from tobacco when in withdrawal (Jacobsen et al. 2007). Moreover, an ecological momentary assessment study found that when cannabis and tobacco are combined, working memory performance was better in comparison to cannabis alone (Schuster et al. 2016). It may also be that cannabis increases urge or craving to smoke tobacco, and vice versa, as suggested by preclinical research (Solinas et al. 2007b). However this hypothesis has never been explicitly tested, although has been reported in qualitative research (Amos et al. 2004).

There is also pre-clinical evidence to support the hypothesis that tobacco may compensate for some of the negative effects of cannabis on memory. As reviewed in section 1.2.5.3, there is overlap between the eCB and nAchR systems and significant interactions between cannabis and tobacco have been found in preclinical research. Exposure to nicotine, for example, can increase CB1 expression in the rodent hippocampus, and this increase persists for a month after nicotine cessation (González et al. 2002). Moreover, cannabinoid agonists increases efflux and changed turnover of acetylcholine in the hippocampus (Viveros et al. 2006) (Viveros et al. 2006).

To my knowledge, no controlled studies have yet examined whether tobacco can offset the cognitive impairing effects of cannabis.

1.3.5 Psychotomimetic effects of co-use

Epidemiological research has implicated both cannabis and tobacco as independent risk factors for psychosis (see sections 1.1.6 and 1.2.4) (Gurillo et al. 2015; Moore et al. 2007). As discussed before, both cigarette smoking and problematic cannabis use are both highly prevalent in people with schizophrenia (de Leon and Diaz 2005; Koskinen et al. 2010). However, it can be extremely challenging to dissociate the role of cannabis from tobacco in epidemiological studies due to the high co-occurrence of their use (i.e. cannabis users are more likely to smoke cigarettes and cannabis and tobacco are often combined and smoked together) (see section 1.3.2) (Gage et al. 2014). Acutely,

cannabis/THC induces psychotic-like effects, including paranoia, disorganised thinking and hallucinations. However, there is no experimental evidence that nicotine/tobacco induces or exacerbates psychotic-symptoms acutely (Smith et al. 2006). One study investigated the acute effect of a nicotine patch on cannabis induced psychotomimetic effects (using the Addiction Research Center Inventory: LSD subscale) where nicotine had no effect on THC (Penetar et al. 2005). Thus, given the high prevalence of combined use of cannabis and tobacco, it is necessary to understand their interactive effects on psychotic-like symptoms.

Until recently, tobacco was considered a confound between cannabis use and psychosis, as those who are likely to smoke cannabis and likely to smoke tobacco. However, epidemiological research suggests when you exclude all cannabis users, age of first tobacco users was still related to psychotic-like experiences and hallucinations (McGrath et al. 2016). In population survey research, the relationship between cannabis and psychosis as well as between tobacco and psychosis were equivalent, and the cannabis-psychosis relationship was significantly weakened when controlling for tobacco (van Gastel et al. 2013). This was also evident in data from the AVON longitudinal survey where both cannabis and tobacco use at age 16 was predictive of psychotic like experiences at age 18 (Gage et al. 2014). Recently, Jones et al. (2018) found a stronger association for cannabis than for tobacco, however, the authors did not control for combined use. It is very difficult to dissociate cannabis from tobacco in the aetiology of psychosis as many individuals smoke both in joints. However, this is possible in controlled experimental studies of the acute effects of both drugs, versus each individually.

1.3.6 Reward related effects of co-use

Although both drugs have reinforcing effects (Justinova et al. 2008; Shoaib et al. 1997), the cumulative probability of developing dependence across one's lifetime is 67.5% for tobacco users, and 8.9% for cannabis users, suggesting that tobacco is more addictive

than cannabis (Lopez-Quintero et al. 2011). Individual effects on reward processing have been reviewed in 1.1.7.1 and 1.2.5.1.

Preclinical data suggests a functional and bidirectional relationship between the cannabinoid and cholinergic systems that may be mediated by structures involved in motivation (Cohen et al. 2002). For example, prior exposure to THC increases the addictive effects of nicotine (Panlilio et al. 2013b). Furthermore, subthreshold doses of both cannabis and tobacco produce CPP, when individually, they do not suggesting a synergistic effect on reward processing (Valjent et al. 2002). The CB1R is critical to the rewarding effects of nicotine, such that in CB1R Knock-Out mice, the rewarding effects of nicotine are null (Castañé et al. 2002). Indeed, there has been a mass of research that suggest that endocannabinoid system modulates the effects of nicotine and nicotine dependence (for reviews see: Cohen et al. 2005; Le Foll and Goldberg 2005; Scherma et al. 2016).

On the other hand, the role of the nicotine system in THC reward has been less investigated. Solinas et al. (2007a) found that drugs that modulate nAChRS effect the discriminative ability of THC, which is a measure of drug reinforcement. Moreover, they found that this was specifically related to increases in anandamide. Further research by Solinas et al. (2007a) found that blocking nAChRS decreased THC-induced dopamine elevations in the shell of the NAcc. To our knowledge, there has been no research on how combined cannabis and tobacco may influence aspects of reward processing related to these drugs in humans or in rats.

In regards to human research, in my own previous research, I looked at the mediating effect of cigarette smoking on the relationship between cannabis use frequency and cannabis dependence score on the Severity of Dependence scale (SDS) in 300 cannabis users. I found that cigarette smoking, over and above cannabis use, predicted dependency scores in a cross-sectional design, overall accounting for 29% of the variance in cannabis dependence. In a small opportunistic longitudinal follow up (n=65)

of these users, this association was not observed with only baseline cannabis use predicted cannabis dependence. Furthermore, I found that frequency of cigarette smoking mediated the relationship between cannabis use and dependence. I concluded that tobacco smoking could be partial driver of cannabis dependence however; this research was not able to account for the tobacco that individuals were putting in their joints, which according to the research reviewed in this introduction, can acutely influence the subjective and cognitive effects of cannabis (Hindocha et al. 2015b) and was cross-sectional in nature. Recent research has replicated this finding with nicotine dependence (in comparison to tobacco use per se) (Dierker et al. 2018).

1.3.7 Treatment of cannabis and tobacco co-use

Understanding cessation of cannabis and tobacco use is essential, and likely to be more complicated than single-product use problems. In the context of increasing use of cannabis and tobacco co-use as a result of legalisation (Wang et al. 2016), and its marked prevalence in the UK, many users acknowledge that they are addicted to both substances and cessation of both may be necessary (Amos et al. 2004). Thus far, most studies of the relationship between cannabis and tobacco have focussed on the initiation and progression of substance use and have all been observational in nature. One study has shown that withdrawal from cannabis and tobacco were equivalent and withdrawal from both concurrently was more severe than each alone (Vandrey et al. 2008). Few have investigated their interactions in regards to cessation.

In a large sample of university students in the US, Masters et al. (2018) found that greater importance was imparted to cigarette quitting than to cannabis quitting amongst co-users, and participants had lower confidence in their ability to quit cigarettes (Masters et al. 2018). This suggests that co-users are a distinct group who have their own challenges in regards to cessation. However, initial studies suggest that interventions focussing on dual cessation by co-users is both desirable and feasible (Becker et al. 2013, Becker et al. 2014).

There have only been 5 studies that have targeted cannabis and tobacco use which report changes in both cannabis and tobacco use (Walsh et al. in prep). The first investigated the feasibility and acceptability of a group cessation programme (NRT and varenicline were recommended but not prescribed). In a sample of 77 participants of which 96% were combined users, the authors found that one third of patients achieved abstinence of one or both substances. However, only 5.2% achieved dual abstinence at follow up (Becker et al. 2015; Becker et al. 2013).

Lee et al. (2015) utilised a computer-assisted combination of MET, CM and CBT, however, overall it was mostly cannabis orientated, with optional tobacco modules. Both cannabis and tobacco use decreased. Reporting quality was poor with FTND scores being reported at baseline but not at follow up. The paper reports that 44% achieved cannabis abstinence and 12.5% were tobacco abstinent at the end of 12 weeks of treatment. Furthermore, cannabis abstinence did not affect tobacco abstinence (Lee et al. 2015).

Utilising a pharmacological manipulation, Hill et al. (2013) conducted a pilot study with NRT and CBT (no control group or intervention) in individuals with DSM-IV diagnoses of nicotine and cannabis dependence – only 7 out of 12 participants completing 10 weeks of treatment. The analysis only reports on these 7 participants, in whom cannabis 'puffs per day' were decreased and tobacco decreased "meaningfully" (follow-up data for tobacco use was not reported, only that it was "a meaningful decrease").

Adams et al. (2017) recruited 7 participants, who smoke cannabis and tobacco, as part of an opiate detoxification programme. They assessed the effects of varenicline without the use of a control drug (i.e. placebo). They found that participants reported lower cannabis craving, frequency and quantity of use than at baseline, however given the small sample, little can be concluded.

Overall, very few studies with very few participants and poor reporting (as well as inadequate statistical controls) have investigated integrated treatments for both cannabis and tobacco.

1.3.8 Measuring cannabis use, dependence and co-use

There is an implicit assumption regarding cannabis use that the more frequent the consumption, the higher the dose, the more likely dependence is to occur. A key criticism of all research cited in this introduction is that the measurement of cannabis use is limited by how we classify cannabis users and cannabis use; for example how do we define excessive or problematic use? Particularly important for this thesis, is how do we define recreational use? The major key aspects of cannabis use that are not reported include: 1) the strains and potency of cannabis used by individuals in the sample (e.g. skunk vs. resin); 2) use of tobacco in cannabis preparations, which has been shown to almost double the release of THC compared to cannabis alone (Van der Kooy et al. 2009); 3) age of onset of regular use; 4) dose per joint i.e. quantity per administration. This leads to methodological inconsistencies across studies and poor reporting, with inadequate statistical controls, and the under reporting of effect sizes (Temple et al. 2011). Underreporting, as well as the lack of prospective studies and large data sets, are likely to be some of the reasons why the field still has limited insight into the effects of cannabis on the brain.

In regards to cannabis use, frequency is given much more import than quantity. Frequency is certainly important and predicts dependence (Curran et al. 2018; Hindocha et al. 2015b) but quantity is often important too. For example, in tobacco research, quantity of tobacco, rather than frequency of tobacco use, predicts respiratory health (Kuschner et al. 1996). Frequency of use is easily measured with a validated scale called the Time Line Follow Back (Robinson et al. 2014; Sobell and Sobell 1992). However, measures to assess quantity have yet to be fully developed – for example, quantity of cannabis use will vary by the ROA and the amount of cannabis in one bowl (in a bong) and one joint combined with tobacco will likely be different. Therefore, in regards to quantity, face validity is lacking.

Lorenzetti et al. (2016) conducted a systematic review of the effects of cannabis on neuroanatomical changes in the brain and found that whilst some papers reported

frequency of use, others provided the number of smoking episodes and some others, the number of joints. These were used as proxies of “dose”. Importantly, Lorenzetti et al. (2016) found that most studies did not investigate the relationship between dose of cannabis (milligrams of THC) and neuroanatomy. Finally, there was preliminary evidence for associations between the dose of THC and CBD levels specifically, with CBD protecting against THC-related damage. Overall, this study suggests that a movement towards actual assessment of dose is necessary – a combination of quantity, frequency and potency, would therefore be best.

1.4 Summary of Chapter 1

In this first chapter, I have summarised research concerning cannabis and tobacco in regards to their prevalence, neurobiology, and effects on cognition memory, psychosis, reward processing and addiction. I have also briefly considered options for treatment. Within these, I highlighted relevant epidemiological and psychopharmacological research. Then I summarised what limited research has been conducted on the effects of co use, which included both concurrent use and combined use and which is a widespread occurrence. There is a clear dearth of research on the combined effects of cannabis and tobacco, and what research has been carried is problematic partly due to the unclear definitions about use. A review of the literature shows that the evidence in support of the relationship between cannabis and tobacco often come from studies with suboptimal study designs for the investigation of a pharmacological interaction (Schauer et al. 2017). The implications of this are also widespread in the context of increasing rates of CUD and related treatment seeking, where the potential role of tobacco is consistently overlooked. Therefore, there is need to conduct clear epidemiological and psychopharmacological research on the role of cannabis and tobacco co use.

I have also reviewed the literature on endocannabinoid involvement in nicotine addiction. This shows how the relationship between cannabis and tobacco could be used in a positive way, by modulation of the endocannabinoid system for the treatment for CUD and TUD. However, there has been a paucity of human research about this and therefore

a vital human translation is necessary before further investigation can take place, especially given the tumultuous history of the use of drugs that effect the endocannabinoid system to treat tobacco use disorder.

Finally, I highlighted problems associated with measuring cannabis and the over-reliance on metrics of frequency of use over quantity of use.

1.4.1 Research questions

Based on the literature reviewed, there are several gaps in our knowledge of the interactions between cannabis and tobacco, especially when these are combined in a joint as well as the use of cannabinoids to treat tobacco related problems. These gaps lead to the formulation of six research questions which will be addressed in the following empirical chapters of this thesis.

1. How do routes of administration of cannabis and tobacco vary across the world and does this influence motivation to quit the use of either drug?
2. What are the individual and combined effects of cannabis and tobacco on memory and psychotic-like experiences?
3. What are the individual and combined effects of cannabis and tobacco on reward processing and craving?
4. How do recreational cannabis and tobacco co-users estimate dose of cannabis and tobacco in joints?
5. What are the effects of CBD, in comparison to placebo, on tobacco withdrawal, craving and attentional bias after overnight abstinence?
6. What are the effects of CBD in comparison to placebo, on attenuation of the cognitive effects of nicotine abstinence?

In the final chapter I will then overview and integrate the evidence gathered in these empirical studies.

Chapter 2: No Smoke without tobacco? A global online survey of cannabis and tobacco routes of administration and their association with intention to quit.

2.1 Introduction

As described in chapter 1, in 2011-2012 68.6% of cannabis users report past month use of tobacco and 17.8% of tobacco users reported past month use of cannabis (Schauer et al. 2016). Furthermore, co-use of both cannabis and tobacco is now more prevalent the cannabis-alone or tobacco-alone, amongst youth aged 12-17 according to data from the US NSDUH − a nationally representative, household interview survey (Schauer and Peters 2018). However, combined use of cannabis and tobacco (i.e. in the same product) has been poorly investigated due to lack of nationally representative data in countries apart from the US, therefore making it impossible to separate out the risks of concurrent in comparison to combined use. This is an important distinction because they lead to differential risk for both cannabis and tobacco dependence, with combined use apparently leading to higher DSM-IV cannabis use in comparison to concurrent use (Agrawal et al. 2009). This may be because combined has a specific exposure to nicotine that is combined with cannabis, leading to the potential of both nicotine and cannabis dependence, and compounded health effects. Even if these combined routes seem to be uncommon, the effects of the intake modes are virtually unknown (Burdzovic Andreas and Bretteville-Jensen 2018).

The route of administration (ROA), and whether this is with (tobacco-based ROA) or without (non-tobacco ROA) tobacco, may play a significant role in the cognitive and health effects of cannabis as discussed in chapter 1. It also can affect the onset, intensity and duration of the psychoactive effects, addictive potential and both negative and positive consequences.

In this study, I provide a worldwide summary of ROAs for recreational use of cannabis using data from the Global Drug Survey (GDS) 2014. Access to a worldwide sample allowed me to utilise data from participants who use a variety of ROAs, which is not possible in single country samples as they are generally homogenous. Furthermore, data from the GDS is unique as it captures the nuances regarding ROAs that is not available from nationally representative data.

I aimed to investigate if ROAs influence desire and motivation to quit cannabis, and tobacco, after adjusting for the confounding effects of frequency of both drugs and demographic variables. Those who smoke cannabis and tobacco have poor cessation outcomes (Peters et al. 2012) and cannabis use itself may act as a barrier to change as there is evidence of a cannabis amotivational syndrome (Bloomfield et al. 2014; Lawn et al. 2016). Motivations related to cessation are important preparatory steps in the quitting process (Prochaska and DiClemente 1982) and are the key in some therapies such as MET (Miller and Rollnick 2012). Moreover, therapies designed to support motivation to quit have an impact on both cigarette smoking cessation (Lindson-Hawley et al. 2015) and cannabis cessation (Nordstrom and Levin 2007). I hypothesized that non-tobacco ROAs (in comparison to tobacco ROAs) will be associated with increased motivation to quit (i) cannabis and (ii) tobacco.

2.2 Methods

2.2.1 Design and participants

The Global Drug survey (GDS) is an anonymous, self-nominating, cross-sectional online survey of drug use, conducted annually, in partnership with global media partners. Participants are recruited through onward promotion and online social networks on websites such as The Guardian, MixMag, The Ziet and other international publications. Demographic information is also collected, including age, gender and country of residence. Data were collected throughout November 2013 and December 2013. Participants were not paid for their participation. Table 2.1 lists the questions used in the online survey.

Table 2.1. List of questions from the GDS used in this analysis

Drug History For cannabis only, tobacco only and tobacco combined with cannabis	Ever used? (Yes/No)
	Age of first use? (In Years)
	Used in the last 12 months? (Yes/No)
	Number of days used in the last 30 days?*
	Used in the last 7 days? (Yes/No)
Route of Administration	Which is the most common way you currently use cannabis? (Select one) a) Smoked in joint with tobacco b) Smoked in blunt with tobacco c) Smoked in pipe with tobacco d) Smoked in bong/water pipe with tobacco e) Smoked in joint without tobacco f) Smoked in blunt without tobacco g) Smoked in pipe without tobacco h) Smoked in bong/water pipe without tobacco i) Smoked using 'bucket bong' j) Smoked using hot knife k) Using vaporizer l) Eating it in food m) Drinking in tea/infusion n) Other
Impact of drug use	Typically, on a day that you use cannabis, how much cannabis do you use? (in grams) How would you rate the overall negative effects when high (rated between 1-10) How would you rate the overall pleasurable effect when high (rated between 1-10)
Intention to use less of each drug For cannabis only and tobacco only	Would you like to use less cannabis/tobacco over the next 12 months? (Yes / Unsure / No) Would you like help to use less cannabis/tobacco over the next 12 months? (Yes / Unsure / No) Are you planning to seek help to use less cannabis/tobacco over the next 12 months? (Yes / Unsure / No)

*Note: The structure of the GDS is personalized based on this drug use history, therefore, if the respondent has never used cannabis, for example, they would not have the opportunity to answer questions regarding cannabis. *Used in table 2.3 as "DPM cannabis, tobacco and tobacco with cannabis".*

2.2.2 Sample

A total of 74864 responses were received. The number of respondents varied across countries, therefore data were only included from countries with ≥ 500 respondents (n=70977; 94.8% of the sample). I took this conservative approach because of reliability considerations i.e. in countries with a small number of respondents - the level of bias

would be greater and there would be less variance. Furthermore, analysis was restricted to respondents who had used cannabis at least once, in the past 12 months (n=33687, 47.4% of the whole sample). This is a low threshold for cannabis use, however I sought to capture a wide range of variation in cannabis use. This sample was selected specifically to be cannabis users, and within this sample I was interested in varying levels of tobacco from no use at all (e.g. vaporizer use), to heavy use (e.g. smoking cannabis and tobacco joints). Moreover, there was no analogous threshold for tobacco as not all cannabis users smoke tobacco and I wanted to capture this. All participants confirmed that they were 18+ years, and gave informed consent. The current study was approved by the joint South London and Maudsley NHS and Institute of Psychiatry Ethics Committee (Appendix A).

2.2.3 Statistical analysis

All analyses were conducted in SPSS version 23 (IBM). Valid percentages are reported rather than absolute values for descriptive statistics to account for missing data. Binary logistic regression was used to assess the effects of cannabis and tobacco, independently and combined, on six outcome variables which were considered a proxy to possible quitting behaviour stages, as they align with the Stages of Change model (Prochaska and DiClemente 1982) with each question requiring more commitment than the last (see table 2.1 “Intention to use less of each drug”). These were analysed in separate models and ‘unsure’ responses were removed from the analysis (there were a total 759 unsure response for ‘seek help to use less cannabis’ and 1819 unsure responses to ‘seek help to use less tobacco’). Participants were not required to answer every question leading to missing data; complete case analysis was used. As each of the motivation-based outcome questions were binary, analysis was undertaken using logistic regression. I included the following *a priori* variables to adjust for possible confounding variables: gender (binary; female as reference group), and age (in years). I then added frequency of cannabis use, frequency of tobacco use and frequency of ‘cannabis combined with tobacco’ use. Finally, I used ‘Most Common Route Of

Administration' (ROA), which was coded dichotomously as either *tobacco ROA* (reference group) (includes joint, blunt, pipe, bong/water pipe, vaporizer with tobacco) or *non-tobacco ROA* (includes joint, blunt, pipe, bong/water pipe without tobacco). Adjusted odds ratios (aORs) and 95% confidence internals (95% CI) are reported for each model. An odds ratio > 1 is suggestive of non-tobacco routes being associated with increased motivation to change in comparison to tobacco routes. Odds ratios < 1 suggest non-tobacco routes being associated with reduced motivation to change in comparison to tobacco routes.

2.2.3.1 Exploratory analysis with demographics

I also investigated the association of ROA with age and gender. I conducted exploratory analyses using the Brown-Forsyth F-test which is robust to violations in homogeneity of variance (and that of unequal sample sizes) to investigate the association between ROA (non-tobacco ROA vs. tobacco ROA), frequency of cannabis use, frequency of tobacco use, quantity of cannabis use, the negative impact of cannabis use, the pleasurable effects of cannabis use, and age of first tobacco use. Moreover, I compared those who used a vaporizer as a non-tobacco ROA and those who use other non-tobacco ROAs on frequency of tobacco use.

2.2.3.2 Exploratory analysis with regular cannabis users

I replicated the results in a sub-population of regular cannabis users who used cannabis >100 days in the last 12 months.

2.2.3.3 Missing data

There were 191 missing responses for 'Would you like to use less cannabis over the next 12 months?', 14484 missing responses for 'Would you like help to use less cannabis over the next 12 months?' and 14456 missing responses for 'Are you planning to seek help to use less cannabis over the next 12 months?'. Missing data for 'Would you like to use less tobacco over the next 12 months' was 3855 responses, 'Would you like help to use less cannabis over the next 12 months' was 10547 responses, and for 'Are you

planning to seek help to use less tobacco over the next 12 months' there were 10432 missing responses. I did not impute the missing data, but instead used valid percentages rather than absolute percentages where missing data occurred.

2.2.3.4 Sensitivity analysis

I did not include the very infrequently chosen non-tobacco routes of 'bucket bong', 'hot knife', 'in food', 'in drink' or 'other' (2.4% total). However, I did repeat the analysis with these variables combined with non-tobacco routes, and replicated the results presented here. I also repeated the results by removing 'cannabis combined with tobacco' as it was highly multicollinear with frequency of cannabis use, however I report results with the frequency of 'cannabis combined with tobacco' predictor as it replicated the result without this variable.

2.3 Results

2.3.1 Global overview of cannabis and tobacco use (Table 2.2)

Inspection of Table 2.2 indicates the final sample were young, with a mean (SD) age of 27.86 (10.39) years. Across individual countries, mean (SD) age ranged from 22.38 (5.95) in The Netherlands to 32.95 (11.52) in Australia. 25.86% of all respondents were female. Gender was skewed towards male respondents. Female respondents ranged from The Netherlands (41.6% female) to Denmark (19.1% female).

Globally, tobacco ROAs were more common (65.6%) than non-tobacco ROAs (32.1%). Within the non-tobacco ROA group, 16.3% of respondents had never tried smoking tobacco independently of cannabis. The most common tobacco ROA was smoking 'joints with tobacco' (61.3%); alternative tobacco ROAs were seldom chosen. The most common non-tobacco ROA was 'pipe' (11.7%) although 'joint' (cannabis only) was comparably frequent (9.5%).

Inspection of table 2.2 suggests considerable global variation. Firstly, tobacco ROAs were the predominant choice across all European countries (ranging from 90.9% in Switzerland to 77.2% in the United Kingdom). Across Europe, frequent adoption of

tobacco ROAs were driven by the typical use of ‘joint with tobacco’. Although a disproportionately greater number of responses were collected from Germany, compared to responses from Portugal, table 2.2 indicates a high level of consistency in the tendency to use tobacco ROAs among European countries.

In contrast, in the Americas (Brazil, United States, Canada and Mexico), the predominant choice is non-tobacco ROAs (88.8% total), ranging from 92.1% in United States to 79.8% in Canada. Within the Americas, there was considerable variation in the most common non-tobacco ROA. ‘Joint without tobacco’ was almost exclusively reported among Brazilian respondents (80.8%), whilst the other counties tended to use a range of options including ‘pipe without tobacco’ and ‘bong without tobacco’. Use of vaporizers was only frequent in Canada (13.3%) and the United States (11.2%).

Respondents from Australasia tended to choose a mixture of tobacco and non-tobacco ROAs. Australian respondents were more likely to choose a tobacco ROA (51.6%), mainly consisting of ‘joint with tobacco’ (37.0%) but also ‘bong with tobacco’ (12.3%). New Zealand respondents tended to choose a non-tobacco ROA (70.2%) that consisted of predominantly ‘pipe without tobacco’ (27.9%), ‘joint without tobacco’ (23.7%) and ‘bong without tobacco’ (15.0%)

Table 2.2 Cannabis and tobacco: Routes of Administration by country

					Routes of administration with tobacco (%)					Routes of administration without tobacco (%)						
Country	Total N	N cannabis used in past year	Age (M(SD))	Gender %female	Joint	Blunt	Pipe	Bong	**Total tobacco**	Joint	Blunt	Pipe	Bong	Vaporizer	**Total non-tobacco**	Other*
Europe																
Austria	1317	750	25.70 (7.49)	23.00	81.0	0.1	0.3	8.0	89.4	3.9	0.1	1.3	1.4	2.0	8.7	2.0
Belgium	2661	1068	25.91 (7.91)	21.80	89.7	0.5	0.0	0.6	90.8	2.9	0.3	1.2	1.3	1.8	7.5	1.9
France	2019	1300	31.19 (11.14)	20.60	83.0	2.0	0.6	1.9	87.5	3.5	1.4	1.3	0.8	4.5	11.5	1.1
Germany	22232	9905	25.30 (7.84)	19.40	80.2	0.1	0.5	6.4	87.2	4.0	0.3	2.9	2.0	2.2	11.4	1.4
Hungary	3164	1173	27.51 (7.04)	19.40	88.0	0.2	0.6	0.5	89.3	2.6	0.1	4.7	2.3	0.3	10.0	0.7
Republic of Ireland	824	472	26.80 (9.19)	27.20	81.0	0.2	0.0	0.2	81.4	4.2	0.7	6.4	4.2	1.8	17.3	1.3
Denmark	1630	1014	27.36 (9.13)	19.10	81.0	0.4	1.7	3.9	87.0	4.1	0.1	2.9	0.9	3.0	11.0	2.0
Portugal	611	308	25.59 (9.00)	27.20	88.5	1.0	0.0	0.3	89.8	6.8	0.0	1.0	0.3	1.7	9.8	0.3
Spain	1298	820	29.38 (9.83)	24.10	85.4	0.4	0.3	0.3	86.4	7.9	0.5	2.6	0.3	1.1	12.4	1.3
Netherlands	2743	1196	22.38 (5.95)	41.60	86.8	0.2	0.1	0.5	87.6	4.1	0.4	2.0	2.0	1.6	10.1	2.3
Switzerland	4972	1961	27.03 (9.02)	21.30	89.7	0.3	0.1	0.8	90.9	3.0	0.5	1.1	0.8	2.1	7.5	1.6
United Kingdom	7174	3725	27.89 (10.34)	23.80	75.5	0.1	0.1	1.5	77.2	6.0	0.5	6.2	4.4	4.1	21.2	1.7
Americas																
Brazil	1065	736	26.39 (8.15)	19.30	6.7	0.3	0.0	0.4	7.4	80.8	2.8	2.1	3.1	2.6	91.4	1.1
United States	6423	4359	32.09 (14.38)	33.10	3.7	0.1	0.3	0.3	4.4	10.7	3.4	48.1	18.7	11.2	92.1	3.5
Canada	834	570	27.83 (11.39)	29.20	10.9	0.4	0.2	4.5	16.0	31.8	0.9	18.7	15.1	13.3	79.8	4.2
Mexico	627	472	26.02 (7.84)	31.30	6.1	0.4	0.4	0.0	6.9	37.8	6.1	40.9	6.7	0.2	91.7	1.3
Australasia																
Australia	5789	1947	32.95 (11.87)	28.50	37.0	0.2	2.1	12.3	51.6	15.4	0.3	9.8	12.8	5.8	44.1	4.3
New Zealand	5614	1911	31.48 (11.52)	35.60	17.2	0.1	0.2	3.2	20.7	23.7	0.5	27.9	15.0	3.1	70.2	9.1
WORLDWIDE	**70997**	**33687 47.4%**	**27.86 (10.39)**	**25.86**	**61.3**	**0.2**	**0.5**	**3.6**	**65.6**	**9.5**	**0.9**	**11.7**	**6.0**	**4.0**	**32.1**	**2.4**

: *consists of non-tobacco non-inhaled routes of administration ('bucket bong', 'hot knife', 'in food', 'in drink' and ‘other’)

2.3.2 Predicting intention to use less cannabis/tobacco from ROA (Table 2.3)

27.2% of all participants wanted to use less cannabis, 16.1% wanted help to use less cannabis, and 4.6% said they were planning to seek help in the next year. For tobacco, 61.1% said they would like to use less tobacco in the next year, 22.8% stated they wanted help to use less tobacco in the next 12 months and 10.2% said they were planning to seek help to use less tobacco in the next 12 months.

The odds for 'desire to use less cannabis' were 0.625 times lower in the non-tobacco ROA group than in the tobacco ROA group. Conversely, non-tobacco ROAs were associated with a 61.5% increase in odds for 'like help to use less cannabis in the next year' in comparison to those using tobacco ROAs. The effects of ROAs on 'planning to seek help to use less cannabis' were not significant. Taken together, these results suggest that tobacco ROAs were not consistently associated with levels of motivation to change individuals' cannabis use.

Among users of both tobacco and cannabis, non-tobacco ROAs were associated with a 10.7% increase in odds for 'desire to use less tobacco'. Consistent with this, non-tobacco ROAs were associated with an 80.6% increase in 'like help to use less tobacco in the next year' in comparison to tobacco ROAs. Finally non-tobacco ROAs were associated with a 103.9% increase in the odds for 'planning to seek help to use less tobacco'. Together, these results suggest tobacco ROAs were consistently associated with reduced intention to use less tobacco.

Table 2.3 Binary logistic regressions for like to use less, like help to use less and planning to seek help to use less, in the next year for cannabis and tobacco

	Cannabis					
	Like to use less		**Like *help* to use less**		**Planning to seek help to use less**	
Variables	aOR	95% CI	aOR	95% CI	aOR	95% CI
Age	0.981[a]	[0.977, 0.985]	1.025[a]	[1.016, 1.034]	1.023[a]	[1.008, 1.039]
Sex	1.108[a]	[1.026, 1.197]	0.870	[0.733, 1.034]	0.970	[0.709, 1.327]
DPM cannabis	1.025[a]	[1.020, 1.030]	1.033[a]	[1.022, 1.045]	1.046[a]	[1.025, 1.068]
DPM tobacco[b]	0.995[a]	[0.992, 0.997]	1.007[a]	[1.000, 1.014]	1.027[a]	[1.013, 1.040]
DPM tobacco with cannabis[b]	1.017[a]	[1.012, 1.023]	1.018[a]	[1.006, 1.030]	0.985	[0.965, 1.006]
ROA	0.626[a]	[0.561, 0.699]	1.615[a]	[1.230, 2.120]	0.849	[0.525, 1.524]
Constant	0.459	-	0.041	-	0.010	-
N	18971		5728		5060	
	Tobacco					
	Like to use less		**Like *help* to use less**		**Planning to seek help to use less**	
Variables	aOR	95% CI	aOR	95% CI	aOR	95% CI
Age	1.019[a]	[1.015, 1.023]	1.047[a]	[1.041, 1.052]	1.059[a]	[1.052, 1.066]
Sex	1.004	[0.934, 1.080]	0.770[a]	[0.690, 0.858]	0.656[a]	[0.555, 0.775]
DPM cannabis	0.997	[0.992, 1.002]	0.996	[0.988, 1.003]	0.998	[0.986, 1.009]
DPM tobacco[b]	1.034[a]	[1.031, 1.037]	1.045[a]	[1.040, 1.051]	1.049[a]	[1.040, 1.058]
DPM tobacco with cannabis[b]	1.000	[0.995, 1.005]	0.996	[0.989, 1.004]	0.990	[0.979, 1.002]
ROA	1.107[a]	[1.003, 1.221]	1.806[a]	[1.556, 2.095]	2.039[a]	[1.638, 2.539]
Constant	0.519	-	0.033	-	0.009	-
N	18315		11042		9275	

Notes: DPM -days per month, aOR- adjusted odds ratio, ROA - route of administration (tobacco-based inhaled route is the reference category), [a] - 95% CI does not cross 1. [b]- Not all respondents had used tobacco or tobacco with cannabis in the last month.

2.3.3 Exploratory analysis

2.3.3.1 ROA associations with age and gender

There was a significant association between gender and ROA ($\chi^2(1)=48.51$, $p<0.001$). More females used non-tobacco ROAs (36.2%) in comparison to tobacco ROAs (63.8%) and more males used tobacco ROAs (68.2%) in comparison to non-tobacco ROAs (31.8%). Moreover, there was a significant difference between the mean age of those using a tobacco ROA (M=26.23, SD=8.48) and those using a non-tobacco ROA (M=30.79, SD=12.76) ($F(1,14622)=1058.94$, $p<0.001$).

2.3.3.2 ROA associations with drug use and impact of drug use

Those using a non-tobacco ROA used cannabis on more days per months (M=13.61, SD=12.13) than those using a tobacco based ROA (M=12.10, SD=11.46) ($F(1,19089)=109.82$, $p<0.001$) and they used more grams per day (M=0.52, SD=1.14), then tobacco ROA users (M=0.42, SD=0.84) ($F(1,12556)=55.05$, $p<0.001$). Moreover, those using tobacco ROAs (M=20.76, SD=11.90) used tobacco more days per month than those using non-tobacco ROAs (M=13.44, SD=13.08) ($F(1,8501)=1362.21$, $p<0.001$) and had started using tobacco slightly earlier (M=14.65, SD=2.80) than those using non-tobacco ROAs (M=15.36, SD=3.26) ($F(1,14149)= 304.62$, $p<0.001$). There were more negative effects associated with the impact of cannabis in those using a tobacco ROA (M=3.19, SD=1.96) in comparison to a non-tobacco ROA (M=2.52, SD=1.70) ($F(1,19957)=846.64$, $p<0.001$). Participants also found non-tobacco ROAs (M=7.52, SD=1.82) slightly more pleasurable than tobacco ROAs (M=7.11, SD =1.84) ($F(1,20413)=356$, $p<0.001$). Moreover a comparison between vaporizer users and other non-tobacco ROA users shows that vaporizer users use tobacco on less days per month (M=9.53, SD= 12.00) than non-tobacco ROA users (M=13.84, SD=13.12) ($F(1,645)=58.87$, $p<0.001$).

2.3.3.3 Exploratory analysis with regular cannabis users (Table. 2.4)

The analysis in section 2.3.2 (table 2.3) was replicated selecting for participants who smoked cannabis >100 days in the last 12 months, in order to investigate ROA associations with motivation to change in regular cannabis users. 14653 participants responded that they had used cannabis in >100 days in the last 12 months (mean age = 28.7; %female = 20.1). 36.3% wanted to use less cannabis, 22.1% wanted help to use less cannabis, and 6.8% said they were planning to seek help in the next year. For tobacco, 64.5% would like to use less tobacco in the next year, 24% wanted help to use less tobacco in the next 12 months and 11.1% were planning to seek help to use less tobacco in the next 12 months.

The odds for 'desire to use less cannabis' were 0.377 times *lower* in the non-tobacco ROA group than in the tobacco ROA group for regular cannabis users. Non-tobacco ROAs were associated with a 40.7% increase in odds for 'like help to use less cannabis in the next year' in comparison to those using tobacco ROAs. The effects of ROAs on 'planning to seek help to use less cannabis' were not significant. This pattern of results replicates the findings in all users.

Non-tobacco ROAs were not significantly associated with 'desire to use less tobacco' in those who smoked cannabis >100 days in the last year. Non-tobacco ROAs were associated with a 61.4% increase in 'like help to use less cannabis in the next year' in comparison to tobacco ROAs and finally non-tobacco ROAs were associated with a 72.3% increase in the odds for 'planning to seek help to use less tobacco'.

These results are mostly consistent with the results in section 2.3. In those who use cannabis >100 days per year, non-tobacco ROAs were not associated with desire to use less tobacco, however, this may be a power issue, as the number of respondents was significantly reduced (See table 2.4)

Table 2.4 Binary logistic regressions for like to use less, like help to use less and planning to seek help to use less, in the next year for cannabis and tobacco for people who smoke cannabis > 100 days in the last 12 months.

	Cannabis					
	Like to use less		**Like *help* to use less**		**Planning to seek help to use less**	
Variables	aOR	95% CI	aOR	95% CI	aOR	95% CI
Age	0.981[a]	[0.976, 0.986]	1.026[a]	[1.015, 1.037]	1.024[a]	[1.006, 1.042]
Sex	0.963	[0.862, 1.076]	0.84	[0.689, 1.024]	0.91	[0.639, 1.296]
DPM cannabis	1.003	[0.997, 1.010]	1.017[a]	[1.004, 1.030]	1.028[a]	[1.005, 1.051]
DPM tobacco[b]	0.989[a]	[0.985, 0.993]	1.005	[0.998, 1.013]	1.027[a]	[1.011, 1.043]
DPM tobacco with cannabis[b]	1.002	[0.996, 1.009]	1.011	[0.998, 1.024]	0.971	[0.951, 1.993]
ROA	0.377[a]	[0.321, 0.444]	1.407[a]	[1.001, 1.978]	0.652	[0.346, 1.230]
Constant	1.560	-	0.081	-	0.025	
N	14653		3546		2979	
	Tobacco					
	Like to use less		**Like *help* to use less**		**Planning to seek help to use less**	
Variables	aOR	95% CI	aOR	95% CI	aOR	95% CI
Age	1.019[a]	[1.013, 1.024]	1.045[a]	[1.038, 1.052]	1.056[a]	[1.046, 1.065]
Sex	0.95	[0.847, 1.066]	0.816[a]	[0.694, 0.958]	0.623[a]	[0.490, 0.793]
DPM cannabis	0.986[a]	[0.980, 0.993]	0.994	[0.985, 1.004]	0.993	[0.979, 1.008]
DPM tobacco[b]	1.024[a]	[1.020, 1.029]	1.039[a]	[1.030, 1.047]	1.047[a]	[1.033, 1.061]
DPM tobacco with cannabis[b]	1.002	[0.996, 1.099]	0.992	[0.983, 1.002]	0.99	[0.976, 1.004]
ROA	1.149	[0.983, 1.342]	1.614[a]	[1.304, 1.996]	1.723[a]	[1.251, 2.372]
Constant	0.869	-	0.046	-	0.012	-
N	8612		5441		4487	

Notes: DPM -days per month, aOR- adjusted odds ratio, ROA - route of administration (tobacco-based inhaled route is the reference category), [a] - 95% CI does not cross 1. [b]- Not all respondents had used tobacco or tobacco with cannabis in the last month.

2.4 Discussion

The aim of this study was to provide a global overview of cannabis and tobacco ROAs and to examine their association with motivation to use less cannabis and tobacco. Our results demonstrate marked global variation in tobacco/non-tobacco ROAs, with distinct patterns across Europe, the Americas and Australasia. Non-tobacco ROAs were consistently associated with increased motivation to reduce tobacco use, although findings with cannabis were inconsistent. I also found those using tobacco ROAs were more likely to be male and younger than those using non-tobacco ROAs.

Notably, the Americas (Brazil, United States, Canada and Mexico) had comparatively little use of tobacco ROAs. In North America, there was relative high use of vaporizers; devices that heat up cannabis electronically, allowing the vapor to be inhaled without combustion (Malouff et al. 2014). The snapshot of high cannabis vaporizer use is significant as they may be less harmful than smoked cannabis (with or without tobacco). They may also be useful for harm reduction for respiratory problems, and possibly tobacco use (Earlywine and Barnwell 2007; Hindocha et al. 2015b; Van Dam and Earleywine 2010). This suggests a low prevalence of tobacco ROAs and a corresponding higher prevalence of vaporizer use in the United States and Canada may be an important predictor of reduced future tobacco consumption among cannabis users in these countries. Indeed, those using vaporizers were using tobacco on fewer days per month in comparison to those using other non-tobacco ROAs in my exploratory analysis.

Recent prevalence statistics show that Oceania, which includes Australasia, has the highest levels of cannabis use (10.3%) (Gowing et al. 2015). Our data suggests in Australia, the process of mixing cannabis and tobacco is used by about half of those smoking cannabis and represents significant nicotine exposure. In New Zealand, on the other hand, tobacco ROAs are less common than non-tobacco ROAs. In comparison to the rest of the world, which tended to have high levels of a single ROA, respondents

in Australasian countries use a variety of ROAs. However, responses were not received from every country worldwide, and analysis was restricted to countries with 500 or more respondents for reliability considerations. Future studies should aim to recruit from additional countries in order to reflect a “truly global sample”. Moreover, certain forms of combined use of cannabis and tobacco are strongly governed by cultural norms and ethnicity (particularly in the US) which might play a role in this association (Golub et al. 2005; Kelly 2006) and could be investigated in future research, in particular, blunts seem to have a specific exposure to nicotine. However, in the present chapter, I focused on age and sex, other covariates, such as alcohol, was not my focus, but future research may need to undertake model-building approaches to ascertain which demographics should be included.

There are few studies that investigate the effects of ROA, but one recent study found those using ‘pure’ cannabis (equivalent to non-tobacco ROAs in the present study) showed *less* problematic cannabis use than those using cannabis combined with tobacco (Baggio et al. 2014). Our results are consistent with this and other previous research suggesting tobacco smoking is more problematic for those who also use cannabis (Agrawal and Lynskey 2009; Ford et al. 2002; Gourlay et al. 1994). I was able to adjust for the frequency of cannabis and tobacco use. Our results suggest tobacco ROAs are associated with a *reduced* motivation to use *less* tobacco and more negative effects of cannabis, which may account for the poor tobacco-related cessation reported previously (Ford et al. 2002; Gourlay et al. 1994). Additionally these results replicate meta-analysis results suggesting co-users also had a lower likelihood of planning to quit tobacco for good (odds ratio = 0.75, 95% CI [0.58, 0.98]) (Ramo et al. 2012). Post-hoc comparisons between those using non-tobacco ROAs in comparison to those using tobacco ROAs suggests those using tobacco ROAs are heavier cigarette smokers, and started using tobacco earlier. Moreover, only 16% of the present sample were using a non-tobacco ROA *and* had never tried tobacco suggesting that within cannabis users, it is rare to have never tried tobacco.

I also found ROA was not necessarily associated with poor cannabis-related motivations for cessation. An alternative explanation for this finding is that I used a low threshold for cannabis use (once in the last 12 months), however, I did account for the increasing cannabis use in our model which included days per month of cannabis use, and predicted motivation to change. Moreover, I replicated the analysis in regular cannabis users and they remained consistent with the initial analysis. Interestingly, those using a non-tobacco ROA were using cannabis on more days per month, more cannabis per day and found non-tobacco ROAs more pleasurable, in comparison to those using a tobacco based ROA, replicating other recent online survey results (Lee et al. 2016). Furthermore Masters et al. (2018) investigated college students aged 18-25 about cognitions related to quitting cannabis, and found that there was a higher importance placed on quitting cigarettes than cannabis, and this was the greatest to co-users than in cannabis alone users. Practically, this may be related to not having an inexpensive filler to use, but it may also be a factor related to low motivations to use less cannabis (Masters et al. 2018). Recent attempts to create cessation programs for co-users seem promising (Becker et al. 2015; Becker et al. 2013) however, in order to tailor tobacco cessation programs for those who smoke cannabis, further emphasis should be on the use of non-tobacco ROAs as this may increase the likelihood and effectiveness of future tobacco quit attempts.

The implications of tobacco ROAs for clinical and public health consequences of cannabis use are significant. The use of both substances leads to poorer outcomes for cessation attempts than for either drug alone, plays a role in the maintenance of cannabis use and leads to more significant cannabis withdrawal in isolation (Budney et al. 2008; Vandrey et al. 2008). Concurrent use is associated with synergistic pulmonary harms and tobacco use significantly increases the risk of malignancy and may independently be associated with an increased risk of developing psychosis (Gurillo et al. 2015). Many cultures have adopted non-tobacco ROAs suggesting it is possible to

for users to ‘enjoy’ cannabis without tobacco and it is noteworthy that countries reporting the lowest rates of tobacco ROAs also reported the highest use of vaporizers.

To our knowledge, this is the first overview of cannabis and tobacco ROAs. Our design afforded us the ability to collect a large sample rapidly, and on an unprecedented variety of ROAs. This methodology has advantages and disadvantages including those surrounding reliability and validity at a population-based level, as discussed elsewhere (Freeman and Winstock 2015; Winstock and Barratt 2013; Winstock et al. 2001). Online surveys are considered a credible vehicle for opportunistic research, and are valuable where current data is scarce, as is the current case. These data therefore provide a snapshot of the use of cannabis and tobacco ROAs, where there is a paucity of epidemiological data (Lee et al. 2016; Malouff et al. 2014). Epidemiological data on the prevalence of certain ROAs, such as vaporization, have yet to be conducted (Budney et al. 2015) and the GDS has the size and cross cultural representativeness that offer insight into the changes occurring in cannabis ROAs. Moreover, longitudinal studies are necessary to identify the patterns in co-use over time as cannabis legalization spreads (Schauer et al. 2016; Schauer and Peters 2018) .

2.4.1 Limitations

Firstly, I used a self-nominating convenient (drug-using) sample using an internet survey that this may have some reliability and validity issues that include the limited ability to generalize to the countries included in our analysis (Winstock and Barratt 2013; Winstock et al. 2001). Therefore these estimates should be treated with caution until replicated, although our data on UK ROAs show consistency with a previous GDS sample of UK cannabis users (Freeman and Winstock 2015). Furthermore, the observed consistency within large geographical regions (especially Europe and the Americas) does lend support to genuine variation; however, our sample was skewed towards people of a young age. I could only capture reliable results from 18 countries, which were mostly western countries; therefore, this research cannot speak to cannabis

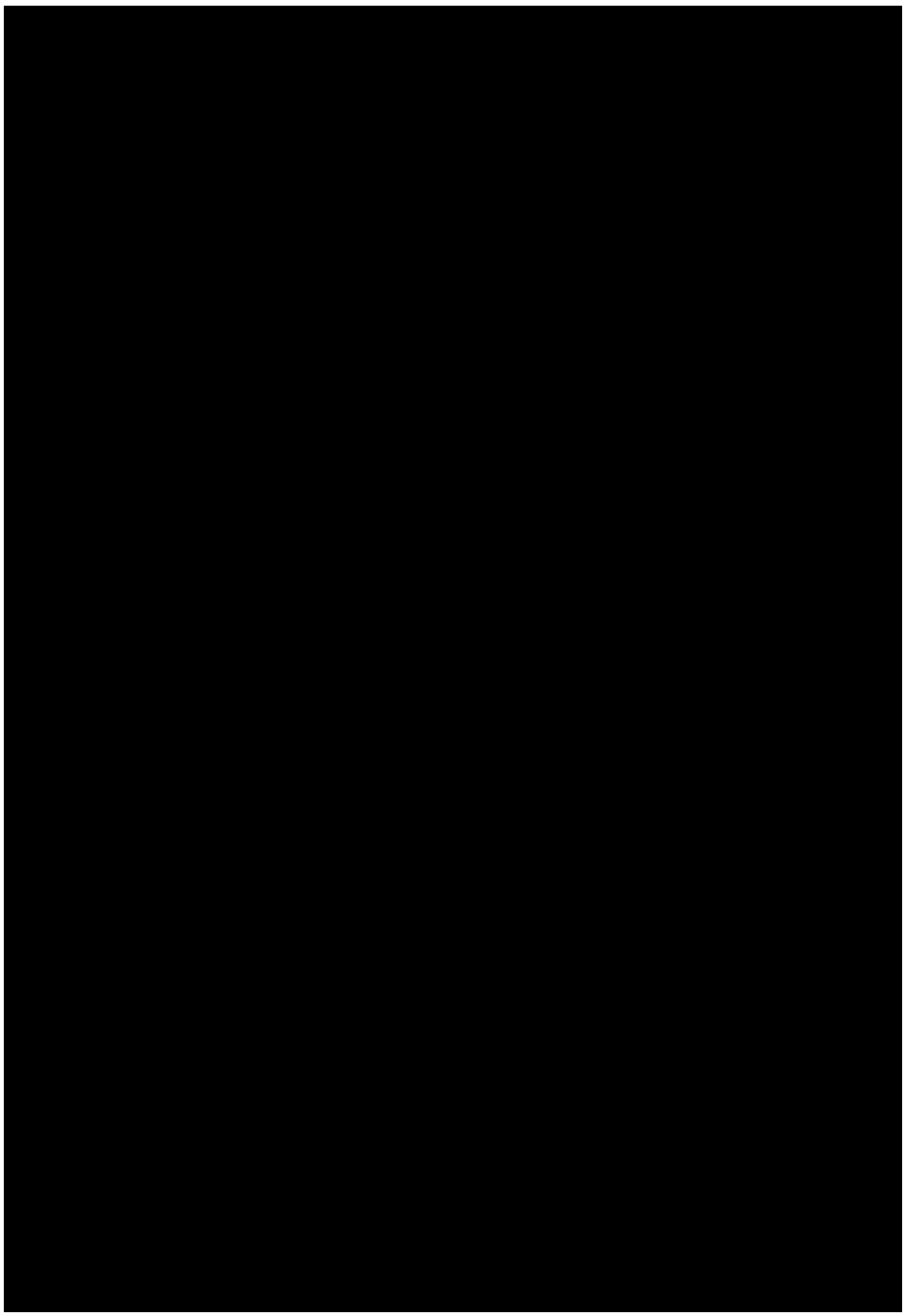
use in non-western counties, wherein 80% of the world's population live. Moreover, self-reported cannabis dependence and/or tobacco dependence was not assessed. Cannabis exposure variables can be poor at predicting cannabis use disorders (van der Pol et al. 2014; van der Pol et al. 2013), the prevalence of which varies worldwide (Degenhardt et al. 2008; Degenhardt et al. 2013). Furthermore, I focused on the hypotheses regarding cannabis and tobacco co-use and did not consider the role of other poly-drug use, including alcohol, which clearly plays an important role or the role of combinations of ROAs (on which there is evidence to suggest the greater the number of ROAs used, the more problematic the cannabis use (Baggio et al. 2014). I modelled three dependent variables each for cannabis and tobacco, which were related to increased motivation to use less of that drug (Prochaska and DiClemente 1982), however these were not clinically validated and can only provide preliminary evidence on motivation to use less of each drug.

Finally, in this chapter I have used different terminology to the rest of this thesis in that I used "tobacco-based ROA" to refer to combined cannabis and tobacco in a multitude of different routes and I use non-tobacco ROA to refer to cannabis used alone.
However, both sets of individuals may also concurrently smoke cigarettes. In these analyses, however, not all respondents had used tobacco or tobacco with cannabis in the last month. As such it would be inaccurate to refer to this as concurrent use.
Finally, the GDS had designed its survey (2013/2014) before I was able to analyse the data (2015/2016), as such I did not want to change the original terminology.

2.4.2 Conclusions

Among a large sample of western cannabis users, tobacco ROAs are frequently adopted. This is especially true in European countries, followed by Australasia, and then the Americas, where non-tobacco ROAs are more common. Non-tobacco ROAs were associated with greater motivation to change tobacco use, and therefore may reduce the harmful consequences of cannabis use.

Chapter 3: Acute memory and psychotomimetic effects of cannabis and tobacco both 'joint' and individually: a placebo-controlled trial.



3.1 Introduction

In chapter 2, I demonstrated that smoking cannabis with tobacco is prevalent in many western countries but there is marked variation in tobacco and non-tobacco ROAs where it was clear that patterns emerged across Europe, the Americas and Australasia. Another clear finding was that the use of joints with tobacco was the most prevalent route of administration. Although this may well influence cognitive and mental health outcomes, this possibility has rarely been investigated in human experimental psychopharmacological research.

Additionally, as I reviewed in chapter 1, cannabis and tobacco seem to have overlapping neurobiology for their respective receptor sites, where they are highly concentrated in the hippocampal, amydgala and striatum. Interactions between the nicotine acetylcholine and endocannabinoid systems may underlie the widespread practise of combining. Pre-clinical research has showed that subthreshold doses of both nicotine and THC do not produce CPP on their own in mice, but when given in conjunction produced a significant CPP (Valjent et al. 2002).

Cannabis and tobacco have some contrasting cognitive effects, especially on memory where cannabis dose dependently is detrimental to episodic and working memory (especially manipulation) (Bossong et al. 2012; D'Souza et al. 2004; Morrison et al. 2009). Nicotine, on the other hand, is a cognitive enhancer and improves memory/attention in both smokers and non-smokers (Heishman et al. 2010; Rusted et al. 2000). This gave rise to the hypothesis that individuals may use cannabis and tobacco because tobacco compensates for the detrimental effect of cannabis on cognition (see section 1.3.4). Currently, however, there is a paucity of human experimental research on psychopharmacological interactions between these two commonly used drugs (Schauer et al. 2017). Indeed, 33% of studies investigating the acute and chronic effects of cannabis on cognition fail to report tobacco use (Broyd et al. 2016).

Both have been have been implicated as independent risk factors for psychosis in epidemiological research. However, there is no experimental evidence that nicotine/tobacco induces or exacerbates psychotic- symptoms acutely. One study investigated the acute effect of a nicotine patch on cannabis induced psychotomimetic effects (using the Addiction Research Centre Inventory: LSD subscale) found nicotine had no effect on THC (Penetar et al. 2005). However, this study lacks the ecological administration method of 'joints' and did not use a scale specific to the psychotomimetic drug effects (Mason et al. 2008). Thus, given the high prevalence of use of cannabis and tobacco, it is necessary to understand the interactive effects on psychotic-like symptoms induced by cannabis.

Thus, the question I addressed was: what are the individual and combined effects of cannabis and tobacco on memory and psychotic-like symptoms? I hypothesised that tobacco would acutely counteract the negative effects of cannabis on working and episodic memory. I directly tested this with an *a priori comparison of* the combination of cannabis + tobacco with cannabis alone. We also hypothesised that cannabis would increase psychotic-like symptoms; how nicotine would influence these was exploratory given the dearth of previous relevant research.

3.2 Methods and Materials

3.2.1 Design and Participants

Medically and psychiatrically healthy, non-dependent but experienced, cannabis and tobacco users were recruited. A randomised double-blind, placebo-controlled four-way crossover trial was used to evaluate the acute effects of cannabis and tobacco, both alone and combined (Table 3.1). Participants attended 4 sessions, separated by at least one-week washout (as this is ≥ 3 times the elimination half-life of THC) (D'Souza et al. 2008; Hindocha et al. 2015a). Washout of nicotine was confirmed by Carbon Monoxide (CO) ≤ 6 (Bedfont Micro Smokerlyser, Bedfont Scientific Ltd, Bedfont, UK). Order of treatment was determined by a balanced Latin square. All participants provided written,

informed consent on each occasion. Ethical approval was given by the UCL Ethics Committee (Appendix B).

3.2.2 Participant Recruitment

Participants were recruited from the community through posters around universities in London and on online notice boards. A flowchart of participant recruitment can be found below.

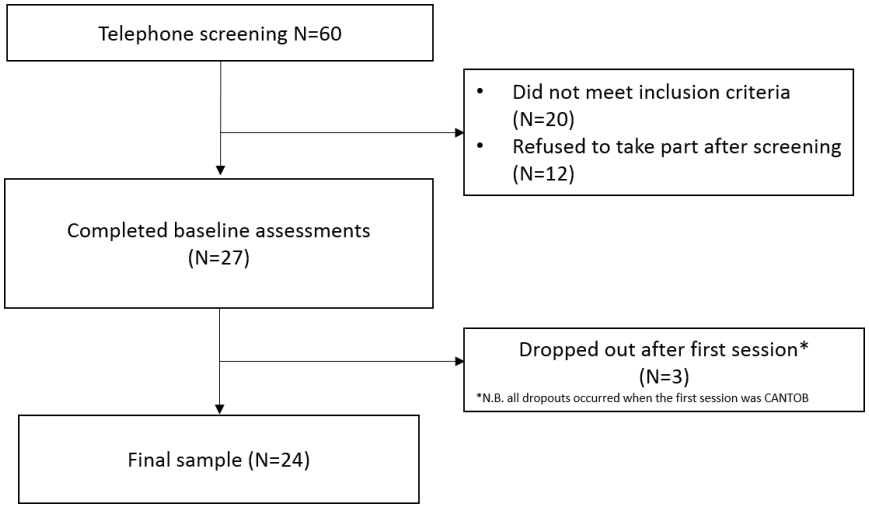


Figure 3.1. Flowchart of participant recruitment. Participants were telephone screened, if inclusion was met, they completed the baseline and first session. 3 participants did not complete the first session and were replaced to meet the final sample of 24 as deemed appropriate from our a priori power calculation (see section 3.2.3).

3.2.3 Power Calculation

Power was informed by a previous four-way crossover trial examining interactive effects of THC and Cannabidiol (CBD) (d=0.5; based on a t-test of THC+CBD attenuating negative effects of THC (Hindocha et al. 2015a)). This estimated a sample size of 24 participants with complete data would achieve power of d=0.5 to detect such effects with an alpha of 0.05 (G*power version 3.1.9.2) (Faul et al. 2007). This was also appropriate for completely balancing the order of the 4 treatments completed the study as 24=4 factorial.

3.2.4 Inclusion criteria

Inclusion criteria were: (i) age 18-60 years, (ii) regular (≥ once per month and ≤ 3 times a week) use of cannabis and tobacco in joints for the last six months, (iii) self-reported (SR) ability to smoke one whole 'standard' joint, (iv) normal or corrected-to-normal vision, (v) fluent English, (v) SR abstinence from tobacco, cannabis, alcohol and other drugs for ≥ 12 hours prior to each session, (iv) alveolar CO ≤ 6ppm to confirm no recent smoking on each test day (Cooper and Haney 2009b). Exclusion criteria were (i) scoring ≥ 3 on the cannabis Severity of Dependence Scale (SDS; Gossop et al. (1995)), (ii) treatment-seeking for cannabis, tobacco use, or currently using nicotine replacement therapy or other cessation pharmacotherapy; (iii) smoking ≥ 10 cigarettes a day or scoring ≥ 4 on the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton et al. (1991)) consistent with previous research (Agrawal et al. 2009), (iv) first cigarette smoked within the first three hours after waking (to ensure cognitive results were not simply due to reversal of withdrawal from tobacco (Jarvik et al. 2000)), (v) significant respiratory, physical or clinically diagnosed learning disorders, (vi) SR diagnosis of a psychotic disorder (or a first degree family member with a psychotic disorder), or substance use disorder, or (vii) SR use of illicit substance use other than cannabis more than once per week.

3.2.5 Drug administration (Fig 3.2/Table 3.1)

We compared the effects of a) active cannabis + active tobacco (**CAN-TOB**) b) active cannabis + placebo tobacco **(CAN),** c) placebo cannabis + active tobacco **(TOB)**, d) placebo cannabis + placebo tobacco (no active drug) **(PLACEBO).** The dose of cannabis specified in Table 3.1 was based on previous experimental studies reporting robust subjective, cardiovascular, psychotomimetic and memory impairing effects (Lawn et al. 2016; Mokrysz et al. 2016).

This dose of tobacco reliably produces peak plasma nicotine levels >20ng/ml (Mendelson et al. 2005; Mendelson et al. 2003) and is similar to a standard cannabis +

tobacco joint (Hunault et al. 2009; van der Pol et al. 2014). Placebo tobacco was the same dose of Very Low Nicotine (VLN; typically referred to as denicotinized) tobacco (Magic 0 (XXII Century Group Ltd)).

Table 3.1. Cannabis and tobacco doses in the study drug and their matched placebos (see Fig 3.1).

Drug	Condition	Description
Cannabis	Active	66.67mg Bedrobinol (16.1% THC and <1% CBD)
	Matched Placebo	66.67mg Placebo (derived from Bedrocan; 0.07% THC)
Tobacco	Active	311mg Marlboro Red (15.48mg/g nicotine, 16mg tar, 0.8mg nicotine yield).
	Matched Placebo	311mg denicotinized tobacco (Magic 0, 0.04mg/g nicotine)

3.2.6 Smoking Procedure

The smoking procedure was standardised to control for dose titration and maximise absorption of THC (Ramaekers et al. 2006). Participants were asked to inhale for 4 seconds, hold their breath for 8 seconds, and then exhale and break for 30 seconds. This sequence was repeated until the joint were smoked up to a designated line (Fig 3.1). This protocol was timed and enforced by the experimenter.

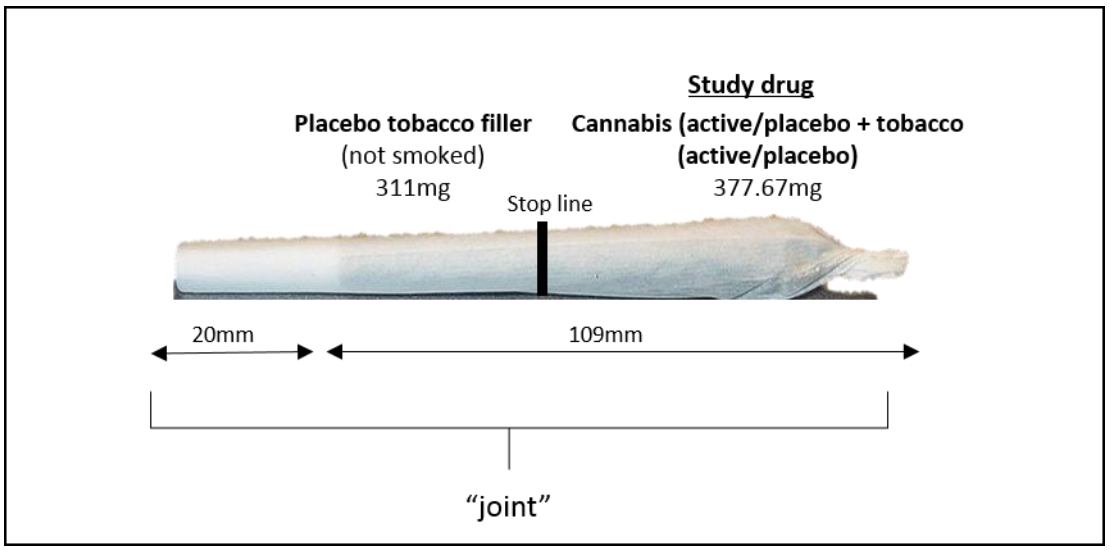


Figure 3.2. Drug administration was conducted using 'joints', the most common method of administering cannabis (see chapter 2). 'Study drug' region contained a mixture of 66.67 mg cannabis (active or placebo) and 311mg tobacco (active or placebo) dependent on condition (see table 3.1). The 'placebo tobacco filler' region contained 311mg of placebo tobacco at the bottom of the joint (nearest to the mouth) which was not smoked. This filler was added to improve compliance with the fixed inhalation procedure as puff volume typically decreases towards the end of the joint, probably due to rising heat (van der Pol et al. 2014). The stop line is the point at which participants stopped smoking the joint, separating the two regions. It was marked 1cm after the 'study drug' to ensure complete inhalation.

3.2.7 Procedure

After telephone screening, eligible participants attended a baseline session involving further screening and task training and then four experimental sessions. Each experimental session began with pre-drug Visual Analogue Scales (VAS), physiological measures and a CO measurement to check abstinence from smoking. Participants then

listened to a passage of prose and were required to immediately recall its content (story 1). Drug administration took place immediately after this. Thirty-five minutes after drug administration, participants listened to a second passage of prose and immediately recalled its contents (story 2). Delayed recall of story 1 and 2 occurred approx. 55 mins after drug administration. Participants completed the N-back and Psychotomimetic States Inventory (PSI; Mason et al. (2008)) at 21 and 45 minutes, respectively (see Fig 3.3). Other tasks that are not reported here took place in the intervening time. Participants were reimbursed £60 for their time and debriefed fully.

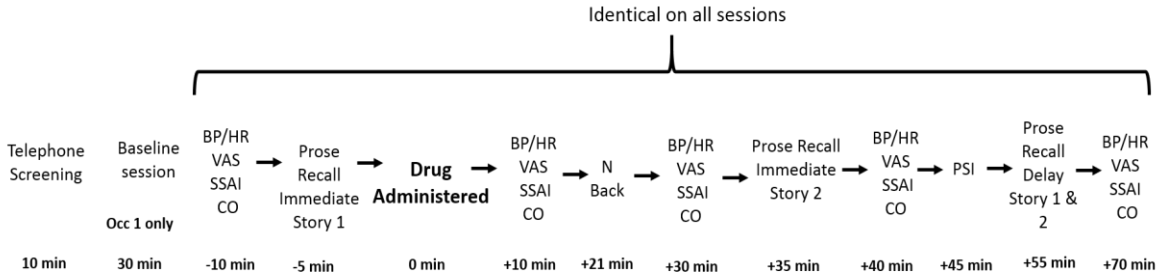


Figure 3.3. Flowchart of Assessments. Other tasks that are not reported here were undertaken at the intervening time points. Post-drug timings are from the beginning of smoking onset. The following abbreviations are used - BP: Blood pressure, HR: Heart Rate, VAS: Visual Analogue Scales, SSAI: Short State Anxiety Inventory, CO: Carbon Monoxide, PSI: Psychotomimetic States Inventory.

3.2.8 Assessments

3.2.8.1 Baseline measures

Participants completed the Beck Depression Inventory (BDI; Beck et al. (1996)), Spielberger State-Trait Anxiety Inventory (STAI; Spielberger et al. (1970)), Schizotypal Personality Questionnaire (SPQ; Raine (1991)), and a detailed drug history including questions about cannabis and tobacco co-use. CO, heart rate (HR), systolic and diastolic blood pressure (BP) and subjective effects were measured pre- (-10) and at 10, 30, 40 and 70 minutes' post- drug.

3.2.8.2 Cognitive measures

3.2.8.2.1 Prose Recall

This is a subtest of the Rivermead Behavioral Memory Test (Wilson et al. 1991) and taps episodic memory. Participants were required to listen to a passage of prose (a 30 second news bulletin) and recall its contents both immediately and after a delay. The first story (1) was heard before drug administration, followed by immediate recall. The second story (2) was heard 35 minutes after drug administration. Delayed recall of both was approximately 55 minutes after drug administration. This design was chosen to dissociate drug effects on encoding from retrieval (Fletcher and Honey 2006). Drug effects on encoding would be evidenced by story 2 (both immediate and delayed) being affected, but not story 1 (i.e. a drug x story interaction). If there were drug effects on retrieval, this would be evidenced by a difference on delayed, but not immediate, recall of story 1 (i.e. a drug x story x delay interaction). Each story contained 21 'idea units' and scoring was systematic. The primary outcome is the mean number of idea units recalled. The 8 versions were counterbalanced across drug and design.

3.2.8.2.2 Spatial N back

Spatial N-back was used to assess spatial working memory. Visual stimuli (smiley faces) appeared in one of six different locations around a central fixation cross on the computer screen, in a sequential order (Freeman et al. 2012b; Morgan et al. 2014). Participants responded by pressing a "Yes" or "No" key according to whether a) the stimuli appeared in a pre-defined location (zero back; attentional control), b) whether the stimulus was in the same position as the stimulus one before (1-back), and subsequently, (c) two before (2-back). Four versions of the task were counterbalanced across drug and design and reaction time and accuracy were recorded.

3.2.8.3 Psychotomimetic effects

The Psychotomimetic States Inventory (PSI) (Mason et al. 2008) was used to assess current schizotypal symptoms. It has 48 items and is specifically designed to measure drug-induced changes in psychotic-like symptoms. It has previously been shown to be sensitive to cannabis-induced psychotomimetic effects and has better test-retest reliability than the Clinician Administered Dissociative States Scale (CADSS; De Simoni et al. (2013)).

3.2.9 Statistical analysis

Data were analysed using IBM Statistical Package for Social Sciences (IBM SPSS version 23). Outliers more than 2.5 standard deviations (SDs) from the sample mean were replaced with a score falling within 2.5 SDs. Normality was explored using visual inspection of diagnostic plots. Data for the Prose Recall, N-back and PSI was analysed using linear mixed models which included a random intercept for subjects and two within subjects factors of drug: Cannabis (placebo; active) and Tobacco (placebo; active). We had additional task-specific factors of Story (1, 2) and Delay (immediate, delayed) for the prose recall and Load (0, 1, 2) for N-back outcomes (correct responses, RT, d', C). VAS scores and physiological factors (HR, BP, CO) had an additional task-specific factor of Time (1 (predrug) vs 2, 3, 4, 5 (postdrug)). The unstructured variance-covariance structure was selected following D'Souza et al. (2012a). Interactions were explored via Bonferroni corrected post-hoc comparisons locally within hypotheses but not across hypotheses (D'Souza et al. 2012a). All descriptive statistics for linear mixed models are estimated marginal means and standard error. d' and C (N-back) were calculated using signal detection analysis (see below) (Snodgrass and Corwin 1988). The loglinear approach was used to account for perfect scores (Hautus 1995; Stanislaw and Todorov 1999). Maintenance was calculated as 1-back minus 0-back and manipulation as 2-back minus 1 back.

Signal detection analysis was used to detect differences in participants' sensitivity and response bias. D prime (d'), a measure of response sensitivity was calculated as d' = z(FA) – z(H) (the standardized difference between the hit rate (signal) and false alarms rate (signal + noise)). Criterion (C) is defined as a response bias to detecting a signal. It was calculated as (-z(FA) + z(H)/2). Larger values of d' mean greater sensitivity (a d' of zero means chance accuracy). Values of C < 1 suggest a liberal response bias, values > 1 are seen as cautious response bias. In the cannabis only conditions, a single participant had 0 hits for all load conditions, however removing them did not affect the analysis therefore they were left in the analysis.

3.3 Results

3.3.1 Demographics and drug history

Twenty-four participants (twelve women), with a mean ± SD age of 24.46 ± 3.96 completed the study. They had minimal dependence on cannabis (SDS: 0.67 ± 0.92 (range: 0-3)) and tobacco (FTND: 0.33 ± 0.64 (range: 0-2)). Those who smoked cigarettes daily (N=6) reported smoking their first cigarette 5.91 ± 3.01 hours after waking. Baseline questionnaire scores were: STAI trait 35.75 ± 8.60; BDI 6.17 ± 5.82; SPQ 19.14 ± 10.83. Other drug use apart from alcohol was minimal (see table 3.2).

Table 3.2. Drug use history (the number of participants varied if they had ever used that drug). Use of other drugs was minimal except for alcohol.

	Alcohol (N=24)	Tobacco (N=24)	Cannabis alone (N=23)	Cannabis+ Tobacco (N=24)	Cocaine (N=17)	MDMA (N=18)
Last used (days)	3.46 ± 3.21	96.125 ± 313.26	466.86 ± 866.37	7.92 ± 9.64	198.46 ± 359.89	295.44 ± 851.03
Age of first use (years)	13.12 ± 2.40	15.71 ± 1.94	16.32 ± 5.41	16.16 ± 3.94	19.80 ± 2.67	19.05 ± 2.98
Years used (years)	9.04 ± 4.57	6.76 ± 4.58	3.31 ± 4.16	6.79 ± 3.94	4.34 ± 3.17	5.50 ± 5.10
Days per month	8.8 ± 5.48	11.04 ± 12.68	0.82 ± 2.09	7.75 ± 4.43	0.41 ± 0.66	0.13 ± 0.34
Amount consumed*	5.88 ± 2.68	2.29 ± 2.74	-	36.58 ± 34.47	331.33 ± 164.78	298.75 ± 240.82
Lifetime exposures (days)	821.04 ± 556.66	2834 ± 7202	49.18 ± 97.60	626.83 ± 935.51	34.65 ± 61.57	42.40 ± 63.92
Exposures in the last 90 days (days)	24.29 ± 17.93	29.75 ± 33.56	3.55 ± 6.39	19.58 ± 11.27	N/A	N/A

*Notes: *For Amount consumed the units vary – Alcohol: units per session; Tobacco: cigarettes per day; Cannabis+Tobacco: Time to smoke an eighth (3.5g) (days); Cocaine: mg; MDMA: mg. Cannabis alone is missing as participants would not smoke a standard 3.5g in this manner.*

3.3.2 Assessments

There were no significant pre-drug differences between the four drug conditions in VAS scores, HR, BP, CO or Short State Anxiety Inventory (SSAI; Marteau and Bekker (1992)).

3.3.3 Time to smoke study joints (Table 3.3)

There were no significant differences between drug conditions on time (minutes) to smoke the joint on each day or number of puffs (see Table 3.3).

Table 3.3. Mean time (mins) to smoke the joint and number of puffs for each drug condition.

	PLACEBO	TOB	CAN	CAN-TOB	Test Statistic
Time to smoke joint (mins)	7.17 ± 1.76	7.95 ± 2.82	6.78 ± 1.17	7.33 ± 1.40	$F_{3,56}$=2.80, p=0.06
Puffs taken	6.96 ± 1.12	7.41 ± 1.41	7.08 ± 1.47	7.27 ± 1.30	$F_{3,63}$=0.80 p=0.50

3.3.4 Prose recall (Fig 3.4)

There was a cannabis X story interaction ($F_{1,23}$=18.51, p<0.001) and a story X delay interaction ($F_{1,23}$=26.60, p<0.001). There were also main effects of cannabis ($F_{1,23}$=10.65, p=0.003) and delay ($F_{1,23}$=107.58, p<0.001) but not of tobacco or story. No significant interaction between cannabis and tobacco emerged ($F_{1,23}$=0.812, p=0.317).

The cannabis X story interaction showed poorer recall following cannabis (M:7.71, SE:0.63) for story 2 in comparison to placebo (M:10.44, SE:0.68) (p<0.001) but not for story 1 (p=0.324). Under placebo cannabis, there was greater recall for story 2 (M:10.44, SE:0.68) in comparison to story 1 (M:8.45, SE:0.51) (p<0.001). By contrast, for active cannabis, there was greater recall on story 1 (M:8.94, SE:0.62), in comparison to story 2 (M:7.71, SE:0.63) (p=0.019).

To test our *a priori* hypothesis that tobacco compensates for the detrimental effect of cannabis on memory compared the difference between CAN-TOB on immediate and delayed recall for story 2 with critical t-tests (Fig 3.4). On immediate recall, there was no difference (t_{23}=1.38, p=0.182) but on delayed recall, scores were significantly higher after CAN-TOB compared with CAN; the mean difference was 1.75 idea units (SD: 3.87) (t_{23}=2.21, p=0.037, d=0.5) (Fig 3.3b)

The story X delay interaction showed that story 2 (M:8.47, SE:0.61) was remembered better than story 1 (M:7.31, SE:0.61) after the delay (p=0.007) but there was no

difference for immediate recall (p=0.360) which suggests a recency effect. The main effect of cannabis (M:8.32, SE:0.56) clearly showed that cannabis impaired recall in comparison to placebo (M:9.45, SE:0.54). The main effect of delay simply showed delayed recall (M:7.89, SE: 0.58) was poorer than immediate recall (M:9.88, SE:0.48).

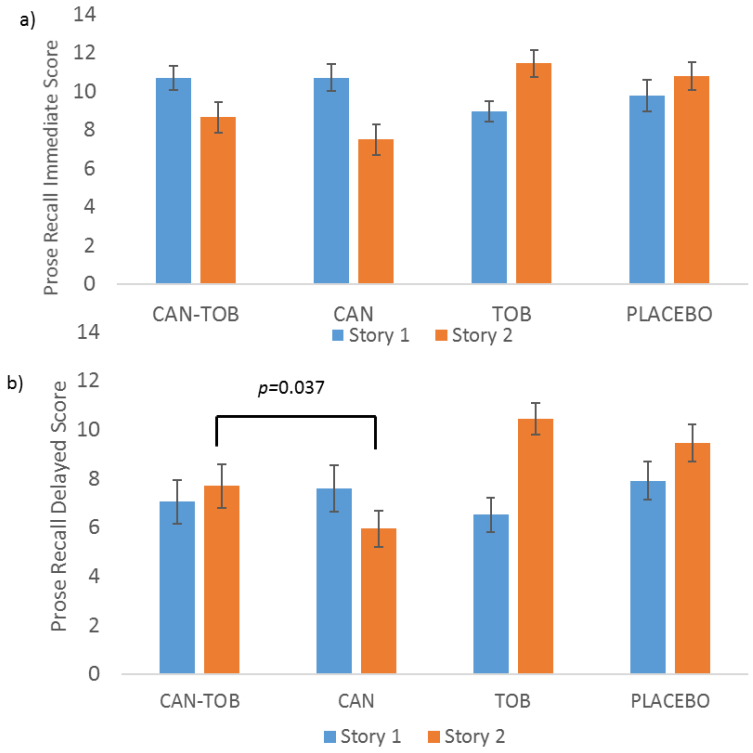


Figure 3.4a-b. Immediate recall (a) and delayed recall (b) under each drug condition for both story 1 (where encoding was not intoxicated) and story 2 (where encoding was intoxicated). Under delayed recall, for story 2, we found CAN-TOB in comparison to CAN, improves delayed recall but this was not the case for immediate recall, therefore suggesting effects on retrieval of information that had previously been successfully encoded. Error bars show ±SEM.

3.3.5 N-back

3.3.5.1 Correct responses (Fig 3.5 a,b)

There was a cannabis X load interaction ($F_{2,23}$=4.82, p=0.018) which showed that cannabis impaired the 1- and 2-back but not the zero-back (Fig 3.5a and table 3.5). A main effect of cannabis ($F_{1,23}$=15.93, p=0.001, reflected better performance on placebo than cannabis and a main effect of tobacco ($F_{1,23}$=4.88, p=0.037) reflected better performance on active tobacco (M:43.77, SE:0.55) than placebo (M:42.58, SE:0.56)

across all load conditions (Fig 3.5b). A main effect of load ($F_{2,23}$=43.42, p<0.001) reflected better performance on 0-back than 1- and 2-back, respectively. No significant interaction between cannabis and tobacco emerged. The critical a *priori* t–test between CAN-TOB and CAN on N-back correct responses across all loads was not significant (p>0.5).

3.3.5.2 Signal detection analysis (Fig 3.5c, d)

3.3.5.2.1 D Prime (D')

There was a main effect of cannabis ($F_{1,23}$=14.48, p<0.001) where cannabis reduced discriminability in comparison to placebo (Fig 3.5c), a main effect of tobacco ($F_{1,23}$=8.25, p=0.009) where tobacco increased discriminability in comparison to placebo (Fig 3.5d) and a main effect of load, ($F_{2,23}$=28.33, p<0.001). The highest discriminability was for the 0-back, followed by the 1-back, followed by the 2-back and there were no significant interactions. The critical apriori t–test between CAN-TOB and CAN on d' averaging over all loads showed a trend towards higher scores with CAN-TOB in comparison to CAN (t_{23}=2.00, p=0.059, d=0.47).

3.3.5.2.2 Criterion (C)

There was a main effect of load ($F_{2,23}$=245.90, p<0.001) whereby the criterion was higher for the 0-back (M:0.50, SE: 0.02), followed by the 1-back (M:-0.04, SE: 0.02) and 2-back (M: -0.06, SE: 0.03).

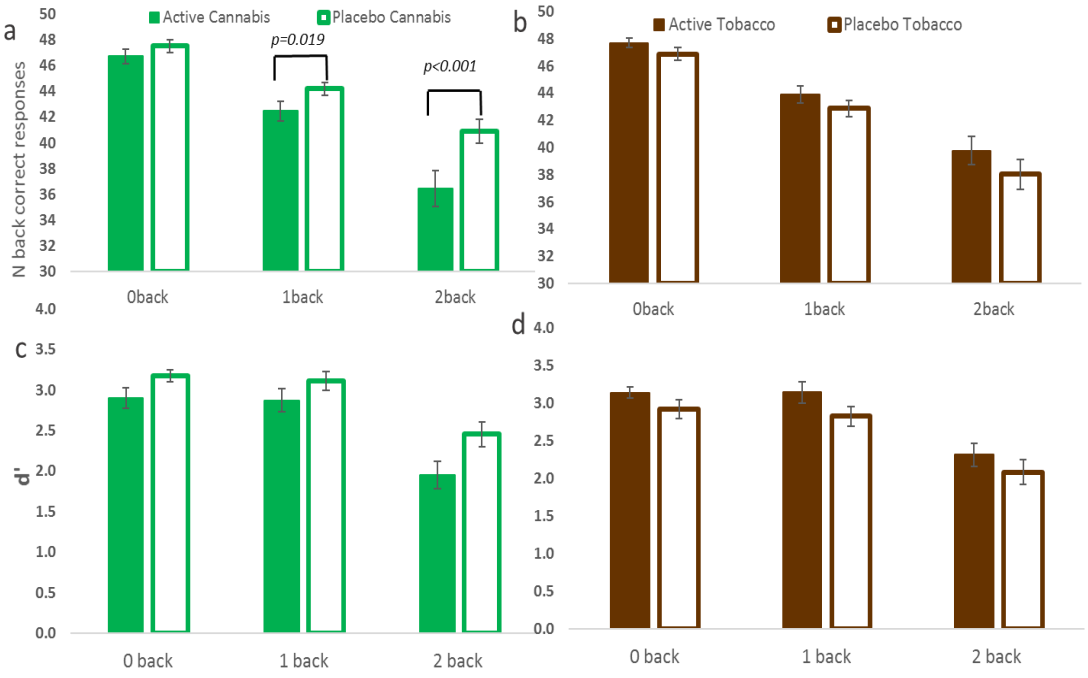


Figure 3.5 a-d. Number of correct responses (a & b) and d' (c & d) for cannabis vs. placebo (a & c) and tobacco vs. placebo (b & d) for the N-back. Error bars show ±SEM.

3.3.5.3 Reaction time

There was a cannabis X load interaction ($F_{2,23}$=8.82, p<0.001) which showed that cannabis impaired the 2-back in comparison to placebo (p=0.005) but not the 1-back (p=0.214) or the 0 back (p=0.979). There was a main effect of load ($F_{2,23}$=68.878 p<0.001) which showed increasing RT across load. There were no main effects or interactions with tobacco.

3.3.5.4 Manipulation and Maintenance

A main effect of cannabis on manipulation ($F_{1,23}$=5.86, p=0.024) showed cannabis impaired manipulation (M:-5.67, SE:1.04) in comparison to placebo (M:-3.27, SE:0.77); there were no other effects or interactions. No main effects or interactions emerged for maintenance.

Table 3.4. Means (SEM) for Number of correct responses, Reaction Time (RT), D prime (d') and Criterion (C) for each drug condition.

	PLACEBO			TOB			CAN			CANTOB		
	0 back	1 back	2 back	0 back	1 back	2 back	0 back	1 back	2 back	0 back	1 back	2 back
Number Correct	47.92	43.63	39.83	47.54	44.75	42	45.83	42.08	36.21	47.83	43	37.54
SEM	0.22	0.59	1.22	0.63	0.52	0.98	0.87	0.95	1.62	0.28	1.02	1.57
RT	417.58	532.96	613.02	457.35	535.08	610.16	445.94	577.5	701.03	429.99	542.61	675.12
SEM	13.13	26.42	28.52	34.34	26.6	34.57	27.81	27.94	44.35	28.04	32.2	43.18
d'	3.19	2.99	2.27	3.15	3.22	2.64	2.66	2.67	1.91	3.14	3.07	1.99
SEM	0.07	0.13	0.2	0.12	0.14	0.17	0.22	0.19	0.23	0.9	0.17	0.2
C	0.51	-0.08	-0.04	0.52	-0.01	-0.11	0.52	-0.01	-0.02	0.44	-0.06	-0.08
SEM	0.03	0.03	0.05	0.04	0.04	0.05	0.04	0.04	0.05	0.04	0.04	0.04

3.3.6 Psychotomimetic States Inventory (PSI) (Fig 3.6)

A main effect of cannabis ($F_{1,33}$=33.01, p<0.001) showed cannabis (M:32.04, SE:3.53) markedly increased PSI scores in comparison to placebo (M:13.85, SE:1.76); there were no other effects or interactions. The same pattern of results emerged when including PSI subscale as an additional factor. Schizotypy has previously been found to predict acute psychotomimetic response to cannabis; therefore, we added SPQ score as an additional covariate. This did not reveal any interactions between SPQ score and drug effect on the PSI.

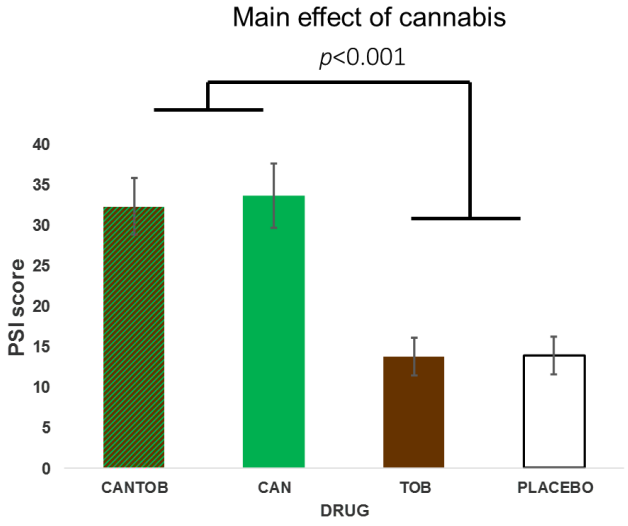


Figure 3.6. Psychotomimetic State Inventory (PSI) score for each drug condition. Error bars show ±SEM.

3.3.7 Physiological measures

3.3.7.1 Carbon Monoxide (CO) (Fig 3.7a)

There was a main effect of cannabis ($F_{1,161}$=4.32, p=0.039) which showed that under active cannabis, participants had a lower CO then under placebo cannabis. There was also a main effect of time ($F_{1,161}$=415.49, p<0.001).

3.3.7.2 Heart Rate (HR) (Fig 3.7b)

A cannabis X time interaction ($F_{1,161}$=62.88, p<0.001) revealed a significant increase on active cannabis, compared to placebo cannabis, post-drug administration (MDiff: 22.71, SE: 2.22, p<0.001), but no difference pre-drug. It also revealed an increase between pre-and post-drug for active cannabis (MDiff: 27.31, SE: 2.20, p<0.001), but not for placebo cannabis. A tobacco X time interaction ($F_{1,161}$=4.49, p=0.036) revealed a significant increase between tobacco and placebo, post-drug (MDiff:6.88, SE:2.20; p=0.002). There was no difference between tobacco and placebo pre-drug. Under both placebo and active tobacco, there was an increase in HR from pre- to post- drug (placebo tobacco MDiff: 11.53, SE: 2.20; p<0.001, active tobacco MDiff: 18.18, SE: 2.20, p<0.001) There were main effects of cannabis ($F_{1,161}$=42.73, p<0.001), tobacco ($F_{1,161}$=5.125, p=0.025) and time ($F_{1,161}$=89.53, p<0.001).

3.3.7.3 Blood pressure (BP) (Fig 3.7c + d)

For diastolic blood pressure, there was a cannabis X tobacco X time interaction ($F_{1,161}$=5.56, p=0.02). All drugs conditions, with the exception of placebo, increased diastolic blood pressure from pre- to post- drug. At the post-drug time point, this manifested in greater diastolic BP under TOB (MDiff: 6.33, SE:1.61, p<0.001) and CAN (MDiff: 6.22, SE: 1.61, p<0.001) than CAN-TOB (MDiff: 1.26, SE: 1.61, p=0.44). There was also a cannabis X tobacco interaction which was explained/subsumed by the above three-way interaction ($F_{1,161}$=5.70, p=0.018). Finally, there was a cannabis x time interaction ($F_{1,161}$=4.64, p=0.033) which revealed a significant that active cannabis

increased diastolic blood pressure, pre- to post- drug (MDiff: 4.51, SE: 1.13; p<0.001), but not under placebo cannabis. There was also a main effect of time ($F_{1,161}$=11.91, p=0.001). There were no other main effects or interaction. For systolic blood pressure, a cannabis x tobacco interaction ($F_{1,161}$=4.65, p=0.03) emerged however pairwise comparisons revealed no significant differences between cannabis and placebo or between pre- and post-drug timepoints.

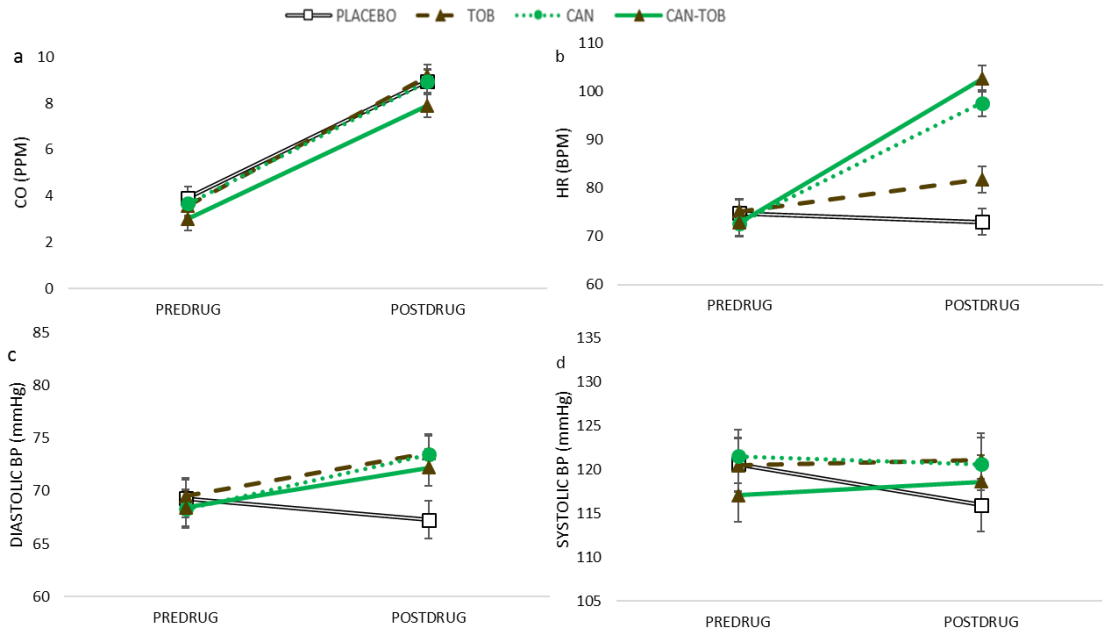


Figure 3.7 a-d. Carbon monoxide (CO), cardiovascular (systolic and diastolic blood pressure (mmHg)) and heart rate (HR) for all time points before (T1) and after (T2-T5) each drug administration. Error bars show ±SEM.

3.3.8 Self-Ratings

3.3.8.1 Stoned (Fig 3.8a)

There was a cannabis X time interaction ($F_{1,161}$=84.59, p<0.001) which revealed a significant increase pre- to post- drug for active cannabis (MDiff: 4.95, SE: 0.31; p<0.001) and for placebo cannabis to a lesser extent (MDiff: 0.91, SE: 0.31; p=0.004). There was no difference between placebo and active cannabis pre-drug, however, there was a significant difference post- drug (MDiff: 4.02, SE: 0.31; p<0.001). There

was also a main effect of cannabis ($F_{1,161}$=82.59, p<0.001) and a main effect of time ($F_{1,161}$=178.25 p<0.001). There were no main effects or interactions with tobacco.

3.3.8.2 Dizzy (Fig 3.8b)

There was a cannabis x time interaction ($F_{1,161}$=17.07, p<0.001) which revealed a significant increase pre- to post- drug for active cannabis (MDiff: 2.41, SE: 0.27; p<0.001) and for placebo cannabis to a lesser extent (MDiff: 0.83, SE: 0.27; p=0.002). Pre-drug, there was no difference between active and placebo cannabis (p=0.817) however active cannabis increased 'dizzy' ratings post-drug (MDiff: 1.51, SE: 0.27, p<0.001). There were significant main effects of cannabis ($F_{1,161}$=17.46, p<0.001), and time ($F_{1,23}$=29.15, p<0.001). No tobacco x time or cannabis x tobacco x time interactions emerged.

3.3.8.3 Lethargic (Fig 3.8c)

There was a cannabis X time interaction ($F_{1,23}$=12.40, p=0.002, η_p^2=0.35) which revealed a significant increase between cannabis and placebo from pre-drug to post-drug. There was a tobacco X time interaction ($F_{1,23}$=6.26 p=0.02, η_p^2=0.21) which revealed a significant increase between tobacco and placebo from pre-drug to post-drug. There were also trends towards a main effects of cannabis ($F_{1,23}$=3.16, p=0.09 np^2=0.12) and tobacco ($F_{1,23}$=4.17, p=0.05, η_p^2=0.15).

3.3.8.6 Nauseous (Fig 3.8d)

There was a cannabis x time interaction ($F_{1,23}$=16.03, p=0.01, η_p^2=0.41) which revealed a significant increase between cannabis and placebo from pre-drug to post-drug. There were main effects of cannabis ($F_{1,23}$=8.81, p=0.01, η_p^2=0.28) and time ($F_{1,23}$=10.52, p=0.004, η_p^2=0.31).

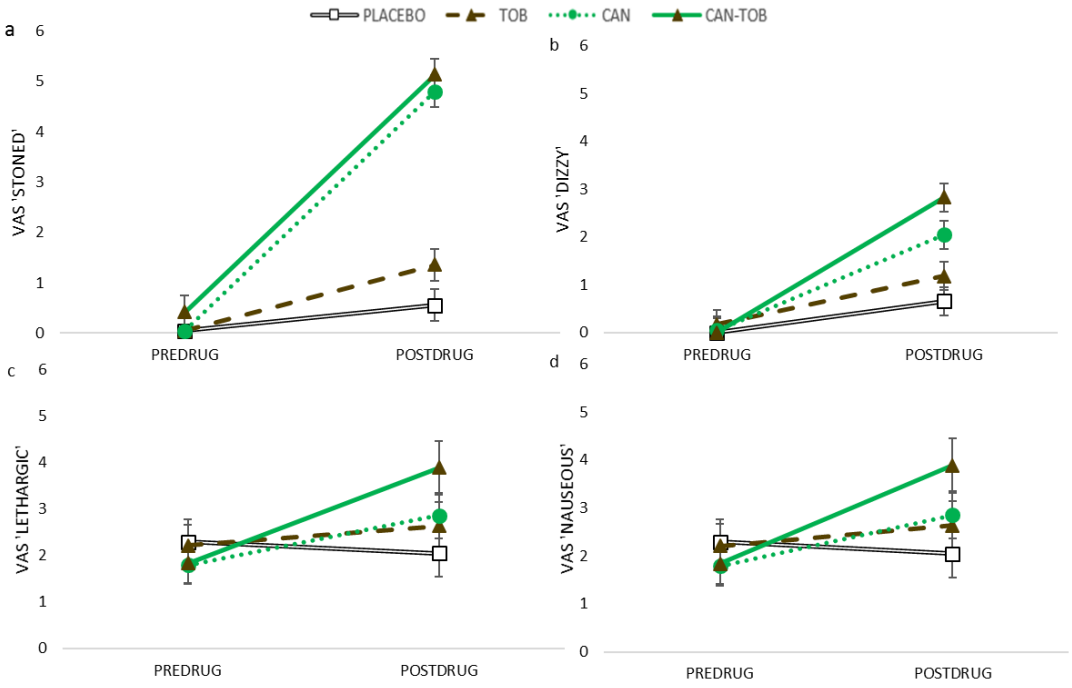


Figure 3.8*a-d. Mean Subjective Ratings as measured by VAS for stoned (A), dizzy (B), lethargic (C) and Nauseous (D) before (T1) and after (T2-T5) each drug administration. Error bars show ±SEM.*

3.4 Discussion

In the first study to investigate the acute interaction between cannabis and tobacco using a controlled randomised crossover design with an ecological method of drug administration, we found that cannabis impairs episodic memory. We found preliminary evidence to support our hypothesis that tobacco would offset the effects of cannabis on verbal recall. However, this finding emerged for delayed but not immediate recall, and was not supported by linear mixed model analysis, so should be treated with caution until replicated. When active tobacco is combined with active cannabis, that impairment in delayed recall is slightly attenuated in comparison to cannabis alone. In regards to working memory, we saw opposite independent effects whereby cannabis was detrimental to working memory, and tobacco improved working memory performance. We also found that tobacco had no effect on cannabis-induced psychotic-like experiences.

In regards to physiological effects, all drug conditions apart from the placebo increased diastolic BP post-drug. Diastolic BP was lower under combined cannabis and tobacco than either cannabis alone or tobacco alone. The biological mechanisms of this effect are uncertain, but warrant further investigation, as combined tobacco and cannabis is the primary route of self-administration. Both cannabis and tobacco had independent effects on HR, with cannabis producing greater increases in HR than tobacco. Tobacco did not influence ratings of 'stoned' or 'dizzy', which are classic cannabis-induced effects. Taken together, we found minimal evidence for interactive effects of cannabis and tobacco in a controlled 2x2 design with an ecological method of drug administration. However, our results tentatively suggest that the common practise of adding tobacco to cannabis in joints (see Chapter 2) may reduce cognitive impairment from cannabis, but does not influence users' psychotic-like experiences or subjective experience of the drug.

Previous research has shown that cannabis acutely induces robust cognitive deficits in working and episodic memory (Bossong et al. 2012; D'Souza et al. 2004; Morrison et al. 2009). Tobacco has been shown to have the opposite effect on the same cognitive constructs but with much smaller effect sizes (Heishman et al. 2010) and both drugs act on receptors that densely populate the hippocampus. The *a priori* comparison on a prose recall task show, although there was no cannabis X tobacco interaction in the linear mixed model analysis, participants performed significantly better after cannabis and tobacco combined than cannabis alone for delayed recall (mean difference: 1.75 idea units) but not for immediate recall. These findings are similar to Englund et al. (2013) who found that THC-induced impairments in delayed but not immediate recall were attenuated by pre-treatment of CBD (Englund et al. 2013). Together, the prose recall and N-back results suggest that tobacco/nicotine increased attentional resources that may be involved in trying to recall information that had previously been encoding correctly. The delayed recall task is more difficult and requires greater attentional resources than the immediate recall task, and these results are in line with the general

improvement effect found on the N-back. These results are also consistent with a recent study of chronic cannabis use, which found a cannabis X tobacco interaction for delayed recall. However, this effect was only evident among those who consistently smoked cigarettes (>100 per year) in comparison to those who sporadically smoked cigarettes (<100 per year) (Schuster et al. 2015). However, this study did not use a controlled design, used a relatively arbitrary cut-off for cigarettes and could not investigate adding tobacco to cannabis in the same product.

In regards to working memory, we found the detrimental effect of cannabis (in comparison to placebo) on the N-back was load-dependent i.e. impairment increased with load, and was selective to manipulation (not maintenance). By contrast, facilitative effects of tobacco on correct responses and discriminability were load-independent, and did not influence manipulation or maintenance, suggesting that tobacco effects are purely on attention. This is consistent with previous function magnetic resonance imaging (fMRI) research showing nicotine altered activity in a neural network associated with task monitoring and attention (Kumari et al. 2003). Our results are consistent with a recent naturalistic study (Schuster et al. 2016) which used a 40-second WM task on mobile phones and found WM was impaired by cannabis, improved by tobacco, and when used in a combined way, participants showed no impairment. Moreover, both Schuster et al. (2016) and the present study did not find evidence for a cannabis X tobacco interaction for WM performance. In the present study *a priori* comparisons between cannabis + tobacco and cannabis alone were only approaching significance for d'. Our findings complement those of Schuster et al. (2016) and provide impetus for further investigation into the interactive effects of cannabis and tobacco on cognition. This study may also provide some mechanistic insights into memory and why both substances may be combined however, it would be essential to replicate this finding in another controlled study. One potential consequence of nicotinic attenuation of the effects of THC on memory may be that it feeds into continued drug taking as certain acute adverse effects are diminished. These results may have relevance to dual

diagnosis populations, for whom rates of both cigarette and cannabis (and tobacco), use are high, presenting an important line of future research.

Tobacco had no effect on feeling 'stoned' or 'dizzy' despite the strongly-held belief that adding tobacco to cannabis increases positive subjective effects (Amos et al. 2004). Although tobacco potentially offset some of the impairing effect of cannabis on memory, this occurred in absence of any positive subjective effects. This is in contrast to previous human experimental research which found that nicotine patch pre-treatment increased reports of feeling stimulated and an amphetamine-like feelings scale (Penetar et al. 2005). However, we found a cannabis x tobacco interaction on diastolic BP, and independent effects of cannabis and tobacco on heart rate, which suggest that combining the two, increases the cardiovascular risk of smoking cannabis (for diastolic BP, the combined was lower than cannabis alone and tobacco alone, however this does not negate the increase in diastolic BP). There is a clear public health implication here, suggesting that smoking cannabis with tobacco does not improve the subjective effects of cannabis, and makes it more harmful to one's physical health.

In relation to acute psychotomimetic effects, we found no modification of PSI scores by either tobacco alone or in combination with cannabis. This corresponds to research that finds nicotine also fails to attenuate ketamine-induced psychotic-like experiences and cognitive deficits (D'Souza et al. 2012a). In recent epidemiological studies, tobacco and cannabis have both been shown to predict the rate of psychotic-like experiences (Gage et al. 2014; van Gastel et al. 2013). Although more recent evidence suggests the relationship may be stronger for cannabis than for tobacco this study was still unable to account for combined use. The relationship between cannabis, tobacco, and psychosis is complicated given tobacco and cannabis use are so strongly correlated. These findings do not negate a possible long-term effect of tobacco on psychosis. However, they suggest that such an association is less biologically plausible than for cannabis, as evidenced by acute drug effects.

3.4.1 Strengths and Limitations

Strengths of this study include a large sample size (informed by an *a priori* power calculation*)*, its double-blind, randomized, double-placebo-controlled, crossover design, and use of well-validated tasks. Furthermore, we selected participants with minimal dependence on tobacco (and cannabis) so the nicotinic facilitation was not purely due to the reversal of withdrawal effects. We used the PSI which has better test-retest reliability than other scales designed to tap psychotic like effects (De Simoni et al. 2013). Pharmacokinetics (PK)/pharmacodynamics (PD) were not measured so we are unable to comment on temporal changes that might have occurred. For example, previous research has shown that nicotine increases the length of the cannabis effect in some participants (Penetar et al. 2005). Furthermore, nicotine effects reduce quicker after administration (Mendelson et al. 2005; Mendelson et al. 2003) than cannabis's effects and we were not able to conduct multiple dosing studies or ideally, an intravenous study (D'Souza et al. 2012a) however the short testing window was designed to capture nicotine's effects. We also discuss the relationship between cannabis and tobacco, however, we specifically manipulated nicotine in the tobacco and it is not fully justified to use these terms interchangeably. Cannabis may be interacting with other psychoactive components of tobacco, and by manipulating nicotine only, we did not capture the full interaction between cannabis and tobacco. Finally, given the novelty of the research, with multiple statistical comparisons of cannabis and tobacco, we would suggest that these findings be treated with caution until replicated.

3.4.2 Conclusions

In conclusion, this study found that cannabis impaired both working and episodic memory. The effects of cannabis on working memory were load dependent, but the effects of tobacco were load independent suggesting a predominantly attentional enhancement. We found preliminary evidence that combining tobacco with cannabis

may offset some of the effects on episodic memory. We characterised the acute subjective and cardiovascular effects of cannabis and tobacco administered together through a shared route of administration (i.e. joints) and found that these effects were similar to cannabis alone. There was no effect of tobacco on cannabis induced psychotomimetic effects.

Chapter 4: Individual and combined effects of cannabis and tobacco on drug reward processing in non-dependent users.

4.1 Introduction

Both cannabis and tobacco have rewarding effects (Justinova et al. 2008; Shoaib et al. 1997) as reviewed in chapter 1, however the cumulative probability of developing dependence is far higher for tobacco (67.5%) than it is for cannabis (8.9%) (Lopez-Quintero et al. 2011). This suggests that if they are smoked together, tobacco may have an influence on the reward-related properties of cannabis. Given that they are often smoked together, this chapter investigates the individual and combined effects of cannabis and tobacco on reward-related outcomes.

As reviewed in Chapter 1, nicotine and THC have an effect on the meso-limbic dopaminergic pathway, which may contribute to their rewarding effects. Preclinical research suggests that the nicotinic and endocannabinoid systems do interact to affect the rewarding or reinforcing of cannabis and tobacco.

In regards to human research, withdrawal symptoms from smoking cannabis and cigarettes are more severe than from either individually (Vandrey et al. 2008) suggesting that these drugs have an additive or synergistic effect on dependence, potentially due to the overlap of symptoms which include irritability and trouble sleeping. Cigarette smoking status predicts relapse to cannabis and abstinence from cigarettes increases self-administration of (even) placebo cannabis in those who smoke both substances (Haney et al. 2013). Moreover, in a recent study of young adults in the UK, it was found that cigarette smoking increased the addictive potential of cannabis as it mediated the relationship between the frequency of cannabis use and dependence on the drug itself (Hindocha et al. 2015b). However, to my knowledge, there has been no research on how combined cannabis and tobacco may influence aspects of reward processing drugs in humans.

Hypothetical purchase tasks can be used a measure of implicit wanting as previously discussed (see section 1.1.7.1 and 1.2.5.1). Most recently, a state version of the

Marijuana Purchase Task has shown sensitivity to experimentally induced craving (Metrik et al. 2016) whereby cannabis demand indices increased and participants became less sensitive to price after a cue-reactivity paradigm (Metrik et al. 2016). However, no study has yet investigated how acute cannabis on its own and in combination with tobacco, affects demand for cigarettes and cannabis.

Explicit liking of drug-associated stimuli also plays a role in the reinforcing value of a drug. It can be indexed by Pleasantness Rating Tasks (PRT) and the response may be related to hedonic processes involved in drug abuse (Morgan et al. 2010a). Acutely, cannabis, compared with placebo, has been found to increase liking of cannabis-related images, compared to neutral images (Metrik et al. 2015). Further the cannabinoid profile can modify attentional bias of cannabis- and food-related stimuli (Morgan et al. 2010a). On the other hand, findings on the relationship between cigarette use and drug and non-drug reward processing have been mixed (Lawn et al. 2015; Mogg et al. 2003; Powell et al. 2002).

It is possible that cannabis and tobacco together may affect the hedonic responses to both drug and non-drug rewards. However, this possibility has not yet been investigated. Both drugs are also implicated in food responses where they have opposite effects: cannabis stimulates appetite, whilst nicotine appears to decrease appetite (Kirkham 2005; Picciotto 2003). In the study reported in this chapter, I use food-related stimuli as a natural reinforcer or 'non-drug' reward and cannabis and tobacco as 'drug' rewards.

The present study aimed to investigate how acute administration of cannabis and tobacco, both alone and combined, would influence demand (for cannabis puffs and cigarettes), explicit liking of pictorial stimuli (cannabis, cigarette, food and neutral) and craving for cannabis, cigarettes and food. I differentiate effects of cannabis, tobacco and their combination on the subjective liking associated with cannabis, cigarette and

food stimuli. It should be noted that the subjective feeling of “high” or “stoned” increased as a result of THC exposure but was unaffected by combined tobacco administration suggesting tobacco was not moderating subjectively rewarding effects (chapter 3). This study is clinically relevant as it investigates acute effects of cannabis and tobacco, both individually and in a potentially at-risk group (non-dependent cannabis and tobacco co-users) thus allowing us to understand the mechanism by which these users may transition to harmful use/dependence.

I firstly hypothesised that administration of either drug alone would reduce demand, liking and craving for that substance because of satiety (e.g. administrating active cannabis would reduce demand/liking/craving for cannabis). Secondly, I hypothesised that administration of one drug would increase demand, craving and liking for the other substance because of the strong association between cannabis and tobacco in individuals who use both together (e.g. administering cannabis *without* active tobacco, would increase demand/liking/craving for tobacco). Finally, I hypothesised cannabis would increase craving/liking of food-related stimuli and predicted the opposite pattern of effects for tobacco.

4.2 Method

4.2.1 Design and Participants

As described in section 3.2.1

4.2.2 Participant Recruitment

As described in section 3.3.2

4.2.3 Power calculation

As described in section 3.3.3

4.2.4 Inclusion Criteria

As described in section 3.3.4

4.2.5 Drug administration

As described in section 3.3.5

4.2.6 Smoking procedure

As described in section 3.3.6

4.2.7 Assessments

4.2.7.1 The Pleasantness Rating Task (PRT)

This task tapped explicit liking and response time to cannabis, tobacco, food and neutral related cues. In this computer-based task, participants were presented with a fixation cross (500ms) followed by four types of pictorial stimuli in a randomised order for 3 seconds. Participants were asked to rate the pleasantness of each image on a scale of -3 (very unpleasant) to +3 (very pleasant). Stimuli were matched on brightness and complexity and included 36 critical trials. Pictorial stimuli for cigarettes involved smoking-related scenes and were used previously by Mogg et al. (2005). Neutral stimuli were taken from the International Affective Picture system (IAPS) (Lang et al. 1999). Cannabis and food pictorial stimuli were expanded from a previous stimulus set (Morgan et al. 2010a). The task design was modified from Metrik et al. (2015). Four versions were used and counterbalanced across drug design. The experiment was built & conducted using Psychopy (Peirce 2007; 2009).

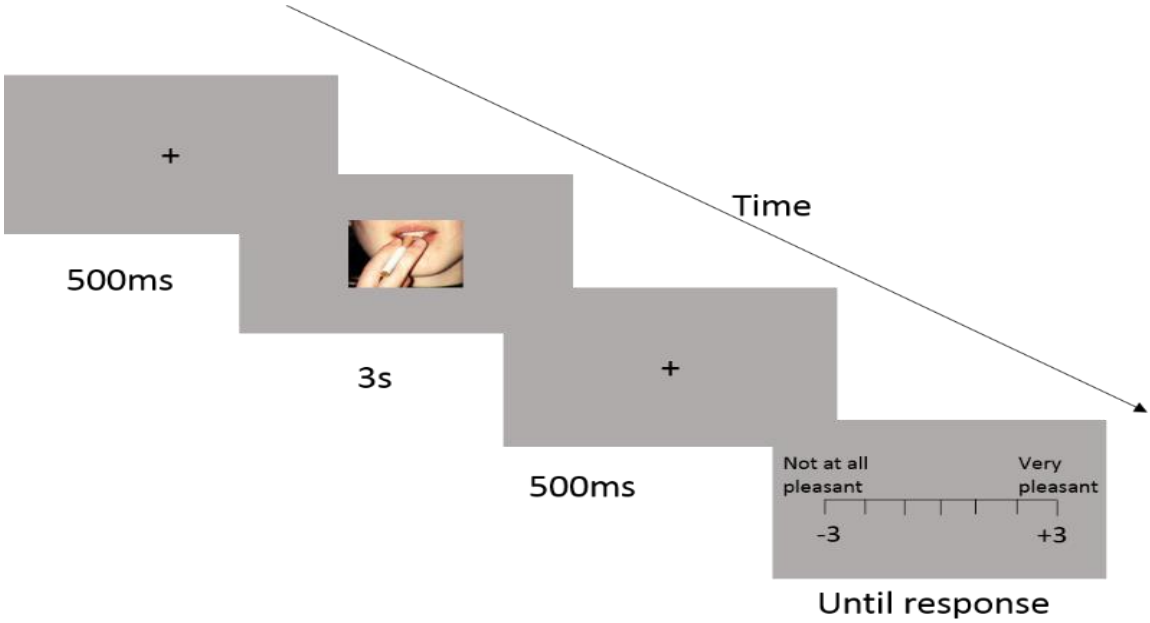


Figure 4.1. Trial structure of the Pleasantness Rating Task

4.2.7.2 The Marijuana Purchase Task (MPT) (Aston et al. 2015; Collins et al. 2014) and Cigarette Purchasing Task (CPT) (MacKillop et al. 2008)

These tasks assess cigarette/cannabis demand i.e. the relationship between cigarette/cannabis consumption and cost (Aston et al. 2015; MacKillop et al. 2008). It is an analogue of a progressive ratio operant task as consumption is investigated under progressively increasing financial cost. It is an established and well-validated task (Aston et al. 2015; Chase et al. 2013; MacKillop et al. 2008; Secades-Villa et al. 2016). In this version, participants were asked how many cigarettes/cannabis puffs they would hypothetically buy in the next 3 hours at increasing prices (Hitsman et al. 2008; Lawn et al. 2017). Specifically they were asked, "How many cigarettes would you smoke if they were _____ each" or "How many puffs of cannabis would you smoke if they were _____each". Prices included: £0 (free), 1p, 2p, 5p, 10p, 15p, 20p, 30p, 40p, 50p, 75p, £1, £1.50 £2, £2.50, £3, £3.50, £4, £5, £7.50, £10, £15, £20 and were presented in that order for both the CPT and MPT. Five indices of cigarette/cannabis demand were generated: breakpoint (cost suppressing consumption to zero), intensity (amount of drug consumed at zero cost), O_{max} (peak expenditure), P_{max} (price at

maximum expenditure) and elasticity (the slope of the demand curve). Importantly, adjustments were made for UK participants for the MPT, including replacing ‘marijuana’ with ‘cannabis’ and ‘hits’ with ‘puffs’.

Instructions for the MPT were the following:

The following questions ask how many PUFFS of cannabis you would purchase at various prices, if they were offered to you RIGHT NOW for over the next THREE HOURS. Assume that you have to smoke all the cannabis that you purchase, and that you cannot get any more cannabis now or after this session. The cannabis is of AVERAGE quality and strength. The joint DOES NOT have any tobacco in it. Answer each question individually, i.e. the number you would buy for price X should not affect the number you would buy for price Y. How many puffs of marijuana would you take RIGHT NOW at the following prices? There are 10 puffs of cannabis in a joint. There is no limit on puffs or joints.

Instructions for the CPT were the following:

The following questions ask how many cigarettes you would purchase at various prices, if they were offered to you RIGHT NOW for over the next THREE HOURS. The following questions ask how many cigarettes you would consume if they cost various amounts of money, assuming that the available cigarettes are your favorite brand and that you have NO ACCESS to any other cigarettes/nicotine now or after this session. The available cigarettes are your favorite brand. Answer each question individually, i.e. the number you would buy for price X should not affect the number you would buy for price Y. You cannot save or stockpile cigarettes for a later date. How cigarettes would you take RIGHT NOW at the following prices? There are no limits on how many cigarettes you can purchase.

4.2.7.3 Craving

This was assessed 'right now' at all five time points with three single item VAS for cannabis, tobacco and food. Each item began with 'I am craving….' with anchors 'not at all' and 'extremely'.

4.2.7.4 Subjective effects

This was assessed 'right now' at all five time points with two single item VAS for euphoric and stimulated. Anchors were "not at all" and "extremely".

4.2.8 Procedure

Each experimental session began with pre-drug VAS for craving and subjective effects. After drug administration, participants completed further VAS for craving and subjective effects at four time points over the next hour as well as the CPT, MPT and PRT (see Fig 4.1). Other tasks that are not reported here took place in the intervening time (see chapters 3 and 5). They were reimbursed £60 for their time on the last test day and debriefed fully. Ethical approval was given by the UCL Ethics Committee (Appendix B).

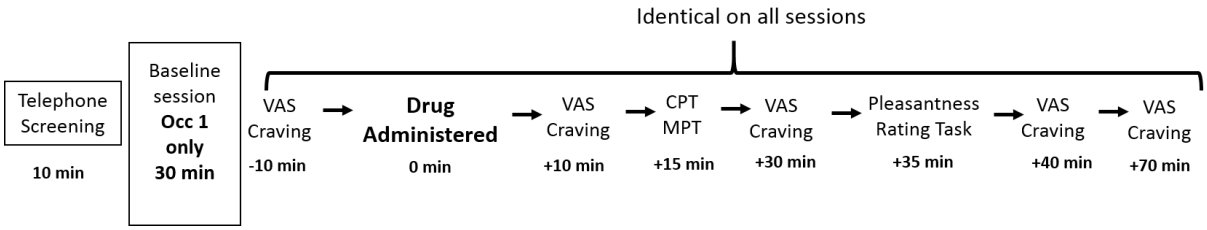


Figure 4.2. Schedule of Assessments. Other tasks that are not reported here were undertaken at the intervening time points. Post-drug timings are from the beginning of smoking onset. Other tasks that are not reported here took place in the intervening time.

4.2.9 Statistical Analysis

All data were analysed using IBM Statistical Package for Social Sciences (IBM SPSS version 23) and GraphPad Prism 7 for Windows (GraphPad Software, La Jolla California USA, www.graphpad.com). For the PRT, outliers >2.5 SD from the sample mean were replaced with a score falling within 2.5 SD of the mean following Das et al.

(2015). Normality was explored using visual inspection of diagnostic plots. When sphericity was violated, the Greenhouse-Geisser correction was used and corrected degrees of freedom are reported. For the PRT, I conducted a 2 (cannabis, placebo) x 2 (tobacco, placebo) x 4 (picture type) repeated measures ANOVA on both valence and response time measures.

Data from the purchase tasks were examined for outliers using standard scores (Z), with a criterion of Z=3.29 to retain maximum data (Tabachnick and Fidell 2000). 0.02% of the data were outliers (Tabachnick and Fidell 2000). The outliers were determined to be legitimate high-magnitude values and were re-coded as one unit higher than the next lowest non-outlying value as per Aston et al. (2015) (Tabachnick and Fidell 2000). Zero-data (i.e. when participants responded that they would not buy purchase any cannabis or cigarettes for 0p/free) was calculated as 41% (39/96 data points) for the CPT and 7% (7/96 data points) for the MPT, and this was due to floor effects post-drug administration. Annual income was considered as a potential covariate but as it did not correlate with demand indices under any drug (p>0.09) it was not included (MacKillop et al. 2012).

Each demand characteristic was analysed using mixed effects models, which accounts for missing data whilst behaving like a repeated measures ANOVA. Cannabis (active, placebo) and Tobacco (active, placebo) were entered as fixed effects and the intercept was allowed to vary randomly. Breakpoint, Intensity, O_{max} and P_{max} were directly observed from the data.

Price elasticity was generated using a modification of the nonlinear exponential demand curve model (Koffarnus et al. 2015): $Q = Q_0 * 10^{k(e^{-\alpha P-1)}}$, where Q=quantity consumed, Q0 =derived intensity, k=a constant across individuals that denotes the range of the dependent variable (cannabis puffs or cigarettes) in logarithmic units, P = price, and α=elasticity or the rate constant determining the rate of decline in log consumption based on increases in price (i.e., essential value). k was fixed to log(80)=1.9 for the

MPT and log(9)=0.9 for the CPT. Q0 was fitted as consumption at 0 pence (free) i.e. Intensity. This is a modification of the Hursh and Silberberg (2008) exponential demand equation and avoids poor model fit because of exclusion of zeros in the equation (Yu et al. 2014).

VAS scores had an additional task-specific factor of time, which was investigated using Helmert contrasts for time (1 (predrug) vs 2, 3, 4, 5 (postdrug)).

4.3 Results

4.3.1 Demographic and drug use history

As described in section 3.3.1. I additionally assessed income as a covariate. Annual income was £14,238.83 ± 10324.83

4.3.2 PRT

4.3.2.1 Valence (Fig 4.3)

There was a cannabis x picture type interaction ($F_{3,69}$=5.35, p=0.002, η_p^2=0.19) which showed cannabis stimuli were rated as less pleasant under active than placebo cannabis (p=0.01; Fig 4.3). Food stimuli tended to be rated as more pleasant under cannabis than placebo (p=0.053; after correction for multiple comparisons). There was a main effect of picture type ($F_{3,69}$=20.68, p<0.001, η_p^2=0.47). Tobacco was rated as unpleasant across all drug conditions and neutral stimuli as around zero valence (neither pleasant nor unpleasant).

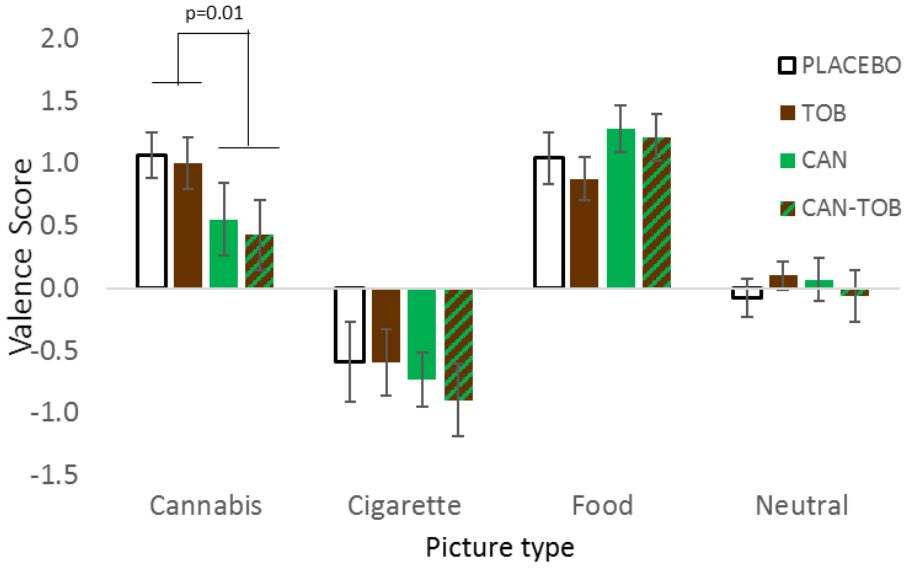


Figure 4.3. Valence score dependent on drug condition for each picture type (error bars show ±SEM).

4.3.2.2 Response Time (Fig 4.4)

A cannabis x picture type interaction ($F_{3,69}$=6.60, p=0.001, η_p^2=0.223) and a main effect of cannabis ($F_{1,23}$=20.33, p<0.001, η_p^2=0.47) were observed. The interaction suggests that cannabis acutely slowed response time across all stimuli apart from cigarette stimuli.

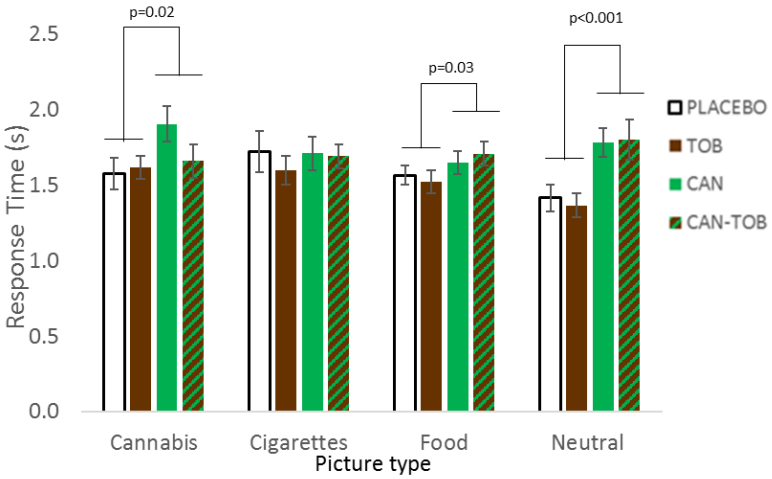


Figure 4.4. *Response time score dependent on drug condition for each picture type (error bars show ±SEM).*

4.3.3 Purchase Tasks

Means (+SEM) for the demand indices derived from the MPT and CPT for each drug condition can be found in Table 4.1.

4.3.3.1 MPT (Fig 4.5)

There was a trend towards a main effect of cannabis on breakpoint ($F_{1,62}$=3.89, p=0.053) where active cannabis reduced the first price at which consumption was zero, in comparison to placebo cannabis (Fig 4.5a). There was a trend towards a main effect of cannabis on elasticity ($F_{1,668}$=2.94, p=0.09), where cannabis increased sensitivity to cost, in comparison to placebo (Fig 4.5b). There were no other main effects or interactions with tobacco for the other demand indices (MPT intensity, O_{max} or P_{max}).

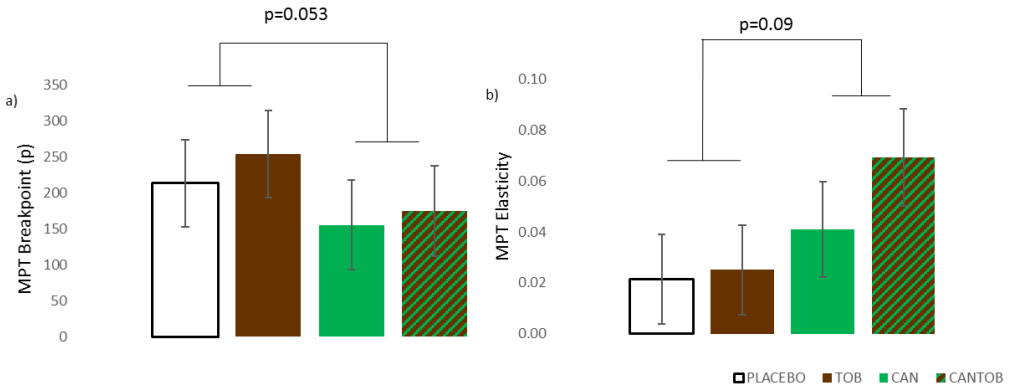


Figure 4.5. Means (SEM) for the demand indices of breakpoint and elasticity derived Cannabis/Marijuana Purchase Task (MPT) for each drug condition

4.3.3.2 CPT (Fig 4.6)

There was a main effect of cannabis on breakpoint ($F_{1,37.37}$=7.00, p=0.01) where cannabis decreased the breakpoint in comparison to placebo (Fig 4.6a). There was a main effect of cannabis for the O_{max} ($F_{1,38.94}$=4.37, p=0.04) (Fig 4.6b) where cannabis reduced the maximum expenditure. There was a trend for a main effect of cannabis for the P_{max} ($F_{1,35.54}$=3.97, p=0.054) where cannabis also reduced the price of the maximum expenditure for cigarettes (Fig 4.6c). For all the above demand indices there was no

interaction with tobacco. There were no main effects or interactions for the other CPT demand indices (i.e. intensity and elasticity).

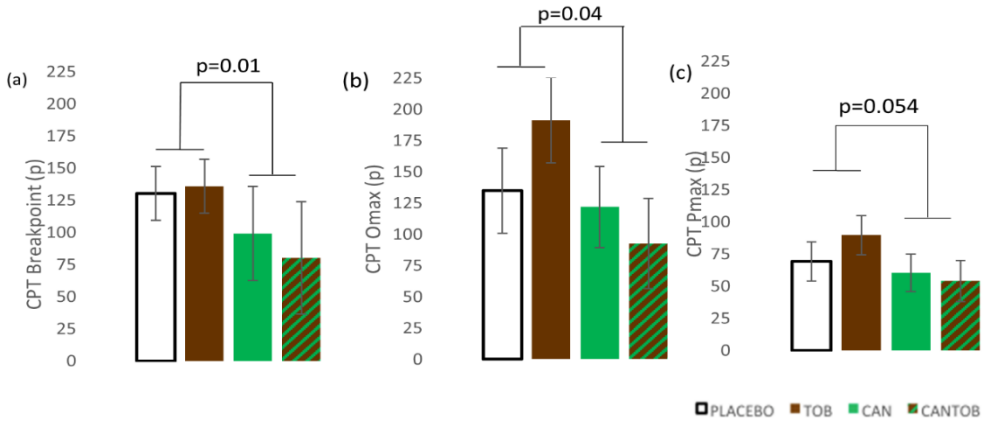


Figure 4.6. CPT indices. There were main effects for cannabis on (a) breakpoint (b) O_{max} (c) P_{max} (trend main effect) (error bars show ±SEM).

Table 4.1. Means (SEM) for the demand indices derived from the Cigarette Purchase Task (CPT) and the Cannabis Purchase Task (MPT) for each drug condition.

	Drug Condition			
	CAN-TOB	**CAN**	**TOB**	**PLACEBO**
CPT				
Breakpoint	81.67 (17.79)	97.19 (19.94)	134.64 (26.24)	139.64 (19.75)
Intensity	4.5 (0.96)	4.00 (0.84)	3.86 (0.73)	3.75 (0.67)
Omax	107.08 (24.78)	122.50 (28.96)	193.57 (53.07)	149.28 (26.49)
Pmax	50 (12.08)	56.56 (13.45)	87.14 (20.18)	76.79 (13.47)
Elasticity	1.65 (0.86)	2.52 (0.78)	1.84 (0.83)	1.03 (0.83)
MPT				
Breakpoint	164.75 (48.99)	145.29 (33.23)	254.63 (84.25)	214.00 (58.40)
Intensity	16.00 (3.52)	17.14 (3.40)	15.63 (2.05)	15.67 (2.29)
Omax	556.00 (143.53)	652.95 (183.86)	621.71 (123.21)	721.87 (162.47)
Pmax	65.55 (3.20)	92.19 (24.21)	81.50 (17.88)	122.50 (41.67)
Elasticity	0.27 (0.19)	0.61 (0.18)	0.11 (0.17)	0.17 (0.17)

4.3.4 Craving

4.3.4.1 Crave Food (Fig 4.7a)

There was a trend towards a main effect of tobacco ($F_{1,23}$=4.11, p=0.054, η_p^2= 0.15); across all time points, tobacco reduced craving for food in comparison to placebo. There was also a main effect of time ($F_{1,23}$=38.58, p<0.001, η_p^2=0.63) so participants craved food more as the test session progressed.

4.3.4.2 Crave Cannabis (Fig 4.7b)

There was a main effect of time (F(1, 23)=5.80, p=0.025 np^2=0.20) but no other main effects or interactions.

4.3.4.3 Crave Tobacco (Fig 4.7c)

There were no main effects or interactions for VAS crave tobacco.

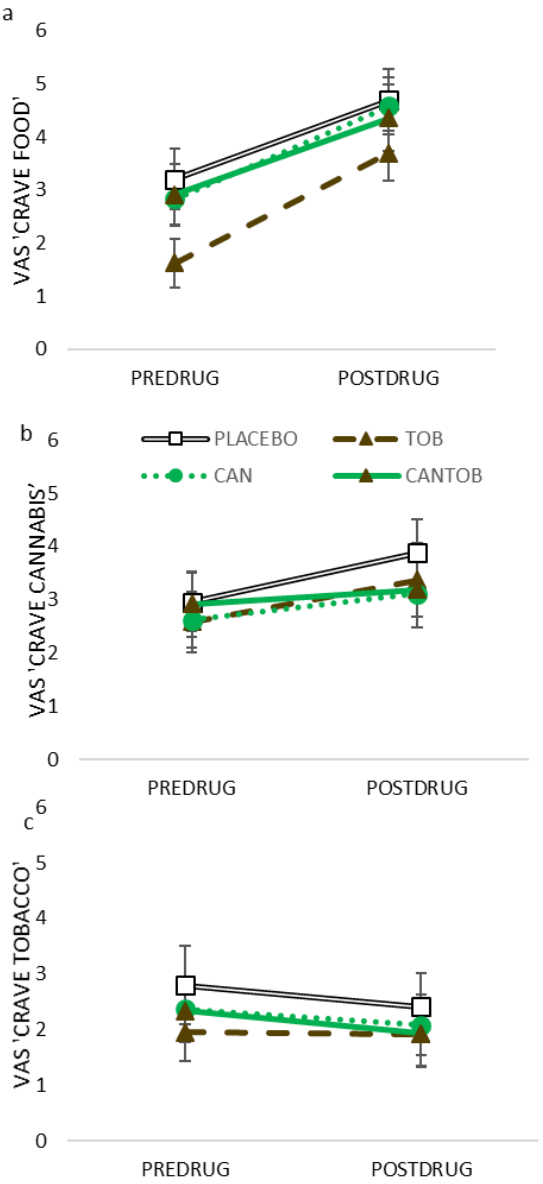


Figure 4.7. Subjective ratings of craving for a) food, b) cannabis and c) tobacco, averaged across all participants for all time points before (T1) and after (T2–T5) each drug administration. Error bars represent ±SEM

4.3.5. Subjective effects

4.3.5.1 Euphoric (Fig 4.8)

There was a cannabis X time interaction ($F_{1,23}$=18.13, p<0.001, η_p^2=0.44) which revealed a significant increase between cannabis and placebo from pre- to post-drug. Pre-drug, there was no difference between active and placebo cannabis (p=0.178)

however active cannabis increased 'eurphoric' ratings at all time-points post-drug (all p's ≤0.004). There was also main effects of cannabis ($F_{1,23}$=10.79, p=0.003, η_p^2=0.32) and time ($F_{1,23}$=12.87 p=0.002, η_p^2=0.36). There were no main effects or interactions with tobacco.

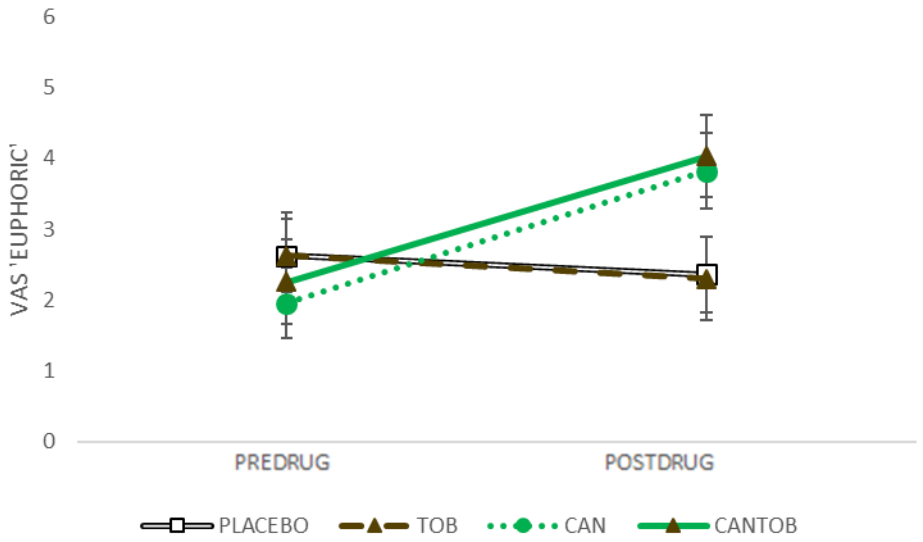


Figure 4.8. Subjective ratings of euphoric averaged across all participants for all time points before (T1) and after (T2–T5) each drug administration. Error bars represent ±SEM

4.3.5.2 Stimulated (Fig 4.9)

There was a cannabis X time interaction ($F_{1,23}$=6.84, p=0.016, η_p^2=0.23) which revealed a significant increase between cannabis and placebo from pre- to post-drug. Pre-drug, there was no difference between active and placebo cannabis (p=0.437) however active cannabis increased 'stimulated' ratings at all time-points post-drug (all p's < 0.05). There was also main effects of cannabis ($F_{1,23}$=5.82, p=0.024, η_p^2=0.20) and time ($F_{1,23}$=11.52, p=0.002, η_p^2=0.33). There were no main effects or interactions with tobacco.

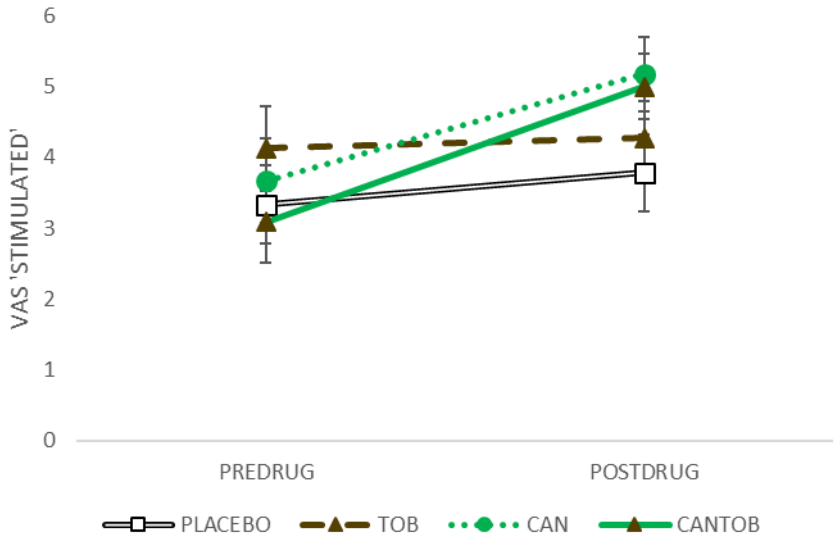


Figure 4.9. Subjective ratings of stimulated averaged across all participants for all time points before (T1) and after (T2–T5) each drug administration. Error bars represent ±SEM

4.3.6 Correlations

Correlations were conducted between valence scores on the PRT and demand indices on the MPT and CPT under placebo only. The valence of cannabis stimuli correlated with CPT indices (breakpoint (r*(24)*=0.55, *p*=0.005); intensity (r(24)=0.63, p=0.001); O_{max} (r(24)=0.58, p=0.003) as well as MPT intensity (r*(24)*=0.60, *p*=0.002).

Correlations were also conducted between craving at T3 and valence scores on the PRT (under placebo). Craving food and liking of food stimuli was correlated r*(24)*=0.63, *p*=0.001). Moreover, craving tobacco correlated with liking cannabis stimuli r*(24)*=0.62, *p*=0.001). Finally, correlations were conducted between craving at T3 and demand indices (under placebo). There were significant associations between craving tobacco and CPT indices (Breakpoint (r*(24)*=0.57, *p*=0.004); Intensity (r*(24)*=0.72, *p*<0.001); O_{max} (r*(24)*=0.55, *p*=0.005).

There were frequently high associations within the demand indices of the CPT and within the MPT as has been found in previous research (Lawn et al. 2017).

4.4 Discussion

To my knowledge, this is the first study to examine both the individual and combined effects of cannabis and tobacco on drug reward processing. I found that, compared with placebo, acute cannabis reduced liking of cannabis- (but not cigarette-) associated stimuli and increased response time to rate all picture types apart from cigarettes. Acute cannabis administration tended to reduce (not significantly), the first point where demand was zero i.e. the breakpoint for both cannabis puffs and for cigarettes, in comparison to placebo. I observed reduced maximum expenditure (P_{max} and O_{max}) for cigarettes, however, this was not significant for P_{max} and therefore should be interpreted with caution until it can be replicated. Overall, this suggests participants under the influence of cannabis became *more* sensitive to price increases and therefore less likely to buy cigarettes or cannabis at higher prices. Smoked tobacco either alone or combined with cannabis did not affect demand indices for cannabis or cigarettes. Taken together, acute administration of cannabis reduced, to a degree, demand for both cannabis and cigarettes. Finally, active cannabis increased ratings of both “euphoric” and “stimulated” but tobacco had no effect on these ratings.

From a public health and clinical perspective, health-focussed campaigns targeting cannabis should emphasise that adding tobacco to cannabis does not modify the reward processing of cannabis and thus users should be dissuaded from mixing cannabis with tobacco. The present results could be a product of cross-satiety between the two drugs because this population use these drugs together like many in Europe such that consuming cannabis also reduces demand for tobacco (Chapter 2).

Moreover, we found a trend towards acute cannabis administration increasing elasticity for cannabis puffs indicating participants were slightly *more* sensitive to the price of cannabis. This is in line with a recent study by Metrik et al. (2016) where experimentally induced craving *reduced* elasticity making participants *less* sensitive to price and suggesting continued purchasing despite price increases (Metrik et al. 2016). The

present results and that of Metrik et al. (2016) are in opposite directions and together show that the state MPT is sensitive to both satiety via acute administration and cue-elicited craving. There were no main effects or interactions with tobacco suggesting that consumption of tobacco does not alter demand for cannabis in this specific context.

Future research should investigate under conditions of cue reactivity, for both cannabis and tobacco, if cross-cue elicited craving occurs, and if there would be a knock-on effect on demand. It should be noted that a possible reason why there was minimal effect on demand for cigarettes is because participants were non-dependent cigarette smokers and little research has been carried out on demand, as measured by purchase tasks, in non-dependent smokers ('chippers') (Shiffman 1989). Investigation of the non-dependent population is an important line of investigation as non-dependent but regular users are vulnerable to the development of addiction and the acute effects of the drugs are not affected by residual drug use or withdrawal.

In the present study, I found that active cannabis reduced liking of cannabis stimuli consistent with research suggesting cannabis users find cannabis-related stimuli more pleasant under placebo than active cannabis (Metrik et al. 2015). Cannabis stimuli were always rated as pleasant (regardless of drug condition) but after smoking active cannabis, the ratings reduced indicative of satiety. Moreover, I found some evidence that cannabis and tobacco had opposite effects on food responses i.e. cannabis tended to increase liking of food stimuli, consistent with classic cannabis-induced 'munchies' and tobacco decreased craving for food, as hypothesised. Interestingly, I did not observe an equivalent effect of food craving, and it is logical that these two would increase concurrently. This may be because the pictorial stimuli of the task were more hunger-inducing than a single-item question. Indeed, food craving did increase steadily over time, but no drug effect emerged. Under all conditions, cigarette stimuli were rated as more unpleasant than all other stimuli, and cannabis slowed response times to all stimuli except cigarettes. This may be because participants had little to no dependence

on cigarettes; however, it may also be due to the negative connotations and stigma associated with tobacco. Young cannabis users often do not consider themselves tobacco smokers even though it facilitates cannabis use and is significantly exposing them to tobacco and its by-products (Bélanger et al. 2011). Perhaps because of their strong negative valence, response times to tobacco stimuli were not modified by acute cannabis. Moreover, it should be noted that neutral stimuli were rated with zero valence, showing that they were indeed rated as neutral.

Future research will be required to investigate if there is a different pattern of results in dependent users of cannabis and tobacco, who may be more sensitive to tobacco cues and this may vary by acute drug intoxication. Future research might also investigate self-administration of individual and combined cannabis and tobacco in humans which would give direct demonstration of the abuse potential of the drugs combined relative to their components – however that was not the aim of the present study.

4.4.1 Strengths and Limitations

This study has several strengths including its sample size informed by a power calculation, an ecologically valid method of drug administration, and factorial investigation of cannabis and tobacco in a double-blind placebo-controlled design. Moreover, I attempted to control for both drugs by asking participants to abstain for at least 12 hours and I was able to confirm this for tobacco with a carbon monoxide level of <6 on each test day. I also attempted to control for food intake by asking participants not to eat for at least two hours before each testing day. However, I was not able to verify (beyond the self-reported SDS) that participants did not have a cannabis use disorder although the mean SDS score was low (0.67 ± 0.92). The lack of effects detected for tobacco are unlikely to be due to an insufficient dose, as I also found that cannabis and tobacco had significant and opposite effects of memory (see chapter 3). Moreover, the lack of effect on reward related measures is unlikely to be due to a negative response to the drug because ratings of ‘euphoric’ and ‘stimulated’ increased

significantly, but there was no difference between combined cannabis and tobacco in comparison to cannabis alone. Moreover, I found that cannabis and tobacco had independent effects on increasing heart rate and interacting effects on increasing diastolic blood pressure (see chapter 3). However, an alternative explanation for these results, is that we had specifically manipulated nicotine, and these results may be a function of the relationship between cannabis and the non-nicotinic aspects of smoking. The doses and route of administration of cannabis and tobacco were designed to be comparable to real-life use and the inclusion criteria of smoking one 'whole' joint is considered a high bar as recreational users mostly share joints. When participants experienced satiety, they stated that they would not buy any hypothetical cannabis puffs, which led to 41% of zero data (i.e. when participant would not purchase puffs for zero pence; floor effects). Though I chose a method of analysis that would allow us to control for this, this is a substantial proportion of the data and therefore these results need to be interpreted cautiously. It indicates the need for more suitable state instruments, which do not result in floor effects because of satiety. Finally, future studies should include comparative purchase tasks for food and validate a purchase task for cannabis-tobacco joints.

4.4.2 Conclusions

Research regarding cannabis and tobacco on addiction-related outcomes is essential. This study aimed to investigate how cannabis and tobacco, alone and combined, would affect validated addiction-related outcomes such as drug demand, explicit liking of associated stimuli and craving, in recreational cannabis and tobacco joint smokers. This study further helps us understand the mechanism by which recreational users may transition to harmful or dependent patterns of use. I found that, acutely, cannabis reduced liking of cannabis stimuli and reduced demand for both cannabis puffs and cigarettes in the purchase task. In this population, tobacco did not influence the

rewarding effects of cannabis. Therefore, health campaigns should try to dissuade users from adding tobacco to cannabis, as it does not make cannabis more rewarding.

Chapter 5: Anatomy of a joint: comparing self-reported and actual dose of cannabis and tobacco in a joint, and how these are influenced by controlled acute administration.

5.1 Introduction

Accurate cannabis use metrics are essential for assessing the effects of cannabis. In the field of alcohol research, the concept of a 'standard unit' exists as a measure of consumption. However, there is no equivalent for cannabis and self-report measures of cannabis use are at best, only weakly correlated with objective measures (van der Pol et al. 2013). Metrics are used mainly as a proxy for exposure to delta-9-tetrahydrocannabinol (THC), but come with many caveats. For example, people often share cannabis and the potency and quantity of the cannabis bought, especially where sales are illegal, is often unknown. Moreover, the quantity of use is likely to be different across types of users, where recreational users are likely to use less cannabis, and therefore potentially more tobacco, than daily users.

The absence of a standardised 'cannabis unit' and methodological differences between studies hinders direct comparisons regarding the effects of cannabis (Lorenzetti et al. 2016; Solowij et al. 2016; Temple et al. 2011; Wetherill et al. 2016). Moreover, the role of *frequency of use* is often overemphasised at the expense of quantity (e.g. amount of cannabis used per day, per joint or joints per gram), which is also a predictor of problematic use (Ridgeway and Kilmer 2016; van der Pol et al. 2013; Walden and Earleywine 2008; Zeisser et al. 2012).

Another major issue is that worldwide, cannabis use is strongly associated with tobacco use (Agrawal et al. 2012; Hindocha et al. 2015b). Particularly in Europe, cannabis is most commonly combined with tobacco into joints as the primary consumption method (see Chapter 2). In Europe, 'joints' typically contain a mixture of cannabis and tobacco (and are interchangeably also referred to as 'spliffs'). Adding nicotine to cannabis may modify its dose by increasing the amount of THC released by almost half (Van der Kooy et al. 2009) as well as affecting the subjective experience (chapter 3; Penetar et al. 2005), cognitive effects of cannabis (chapter 3; Schuster et al. 2016) as well as its rewarding effects (investigated in chapter 4). Combining cannabis and tobacco in joints

could lead to a vulnerability to both nicotine and cannabis dependence (Patton et al. 2005; Schauer et al. 2016). Further, cannabis users titrate (adjust) their dose based on the potency of cannabis therefore modifying their total THC exposure (Freeman et al. 2014b; van der Pol et al. 2014) which means that the dose in a rolled joint may not be the same as the dose consumed. However, thus far, whether cannabis users also titrate their dose to tobacco content has not been investigated.

Several previous studies have investigated dose per joint using a cannabis substitute (Mariani et al. 2011; Norberg et al. 2012; Tomko et al. 2018). The first did not measure tobacco (Mariani et al. 2011); the second used the same substitute to measure both cannabis and tobacco (which have different weights) (Norberg et al. 2012) and neither was conducted with combined users i.e. those who smoke joints with tobacco. The third did not investigate the difference between the amount of substitute placed into the joint, and the participants' guess on grams (Tomko et al. 2018). In one Dutch study, *van der Pol et al. (2013)* estimated dose per joint using actual cannabis, however the amount of tobacco was not estimated. Moreover, there has been no research to date investigating how acute intoxication may influence self-reported and actual dose per joint.

Given the described gaps in the literature and in order to maximise the ecological relevance of this laboratory study, our 'Roll a Joint' procedure used a typical brand of rolling tobacco and a cannabis placebo, produced from active cannabis to contain less than 0.1% THC (sourced from Bedrocan, NL; with the same terpene content, so it retains the look and smells of cannabis). This study was designed to address two specific questions: How do recreational cannabis and tobacco co-users estimate dose of cannabis and tobacco in joints? Secondly, how is estimated and actual dose per joint influenced by smoking cannabis and tobacco, both individually and combined in joints?

5.2 Method

5.2.1 Design and Participants

As described in section 3.2.1

5.2.2 Participant Recruitment

As described in section 3.3.2

5.2.3 Power calculation

As described in section 3.3.3

5.2.4 Inclusion Criteria

As described in section 3.3.4

5.2.5 Drug administration

As described in section 3.3.5

5.2.6 Smoking procedure

As described in section 3.3.6

5.2.7 Assessments

5.2.7.1 Roll a Joint Paradigm

This paradigm was designed as an ecological assessment of participant's a) typical dose per joint (at baseline) and b) desired dose one-hour post- drug administration of both cannabis and tobacco. Ground placebo cannabis (which contains the precise terpene profile of the original strain, with all cannabinoids removed to <0.2% of dry weight; available from Bedrocan NL) and rolling tobacco (Amber Leaf, JTI) were used as substitutes. See section 5.2.9 for full instructions.

5.2.8 Statistical Analysis

Bonferroni corrected paired sample t-tests were conducted between baseline 'actual' and 'estimated' dose to investigate participants' accuracy in guessing dose. Linear mixed models, with a random intercept for 'participant', and two within subjects factors of Cannabis (placebo; active) and Tobacco (placebo; active) were implemented on both actual and estimated dose. The unstructured variance-covariance structure was selected as per chapter 3. The dependent variables of actual and estimated cannabis and tobacco were analysed in separate models.

5.2.9 Procedure

Participants completed the ''Roll a Joint'' paradigm (described in section 5.2.7.1) on the baseline session and at about 1 h after drug administration on each drug session.

Participants were informed that ground placebo cannabis and rolling tobacco were used as substitutes. Two king-sized rolling papers (108mm x 44mm; Rizla Blue) were placed in front of the participant. At baseline, participants were asked to add the 'amount of cannabis and tobacco they would typically put in a joint, if the cannabis and tobacco were of average strength and quality and they could smoke the whole joint by themselves'. One hour after drug administration on each drug occasion, participants measured out cannabis and tobacco in the same manner. They were asked to estimate how much 'the amount of cannabis and tobacco they want to smoke 'right now'. They were then asked to estimate by sight (in g), the amount of cannabis/tobacco in each rolling paper. The weight of the cannabis and tobacco was recorded to the closest 0.01g. Weighing took place under experimenter-blinded conditions and participants were not given any feedback on their accuracy.

All participants provided written informed consent. Ethical approval was given by the UCL Ethics Committee (Appendix B).

5.3 Results

5.3.1 Demographics and drug history

Full demographics and drug use history can be found in section 3.3.1. Twenty-nine percent (n=7) of participants were regular tobacco smokers before they ever combined it with cannabis, 46% (n=11) had tried tobacco, but were not regular smokers, before mixing it with cannabis and 25% (n=6) had never tried tobacco before it was combined with cannabis. They self-reported adding 53.52 ± 19.38% tobacco in their standard joint. They self-reported smoking skunk[1] 49.25 ± 30.74% of the times they smoked cannabis, followed by herbal cannabis[2] (34.7 ± 28.5%) and hash[3] (15.95 ± 14.10%), respectively.

5.3.2 Actual and Estimated dose of cannabis and tobacco per joint

At baseline, there was a significant difference between the *actual* and *estimated dose* of cannabis participants would normally smoke (t_{23}=3.36, p=0.003, d=0.723) where participants overestimated the dose *two-fold.* In contrast, for tobacco there was no significant difference between the *actual dose* and the *estimated dose* (t_{23}=1.59, p=0.125).

Across each drug condition the same effect was observed suggesting participants were accurate in estimating the amount of tobacco (all t's ≥ 0.93, all p's ≥ 0.087) but over-estimated by roughly 200% the amount of cannabis used (all t's ≥ 2.62, all p's ≤ 0.015).

In regards to the *actual dose of cannabis* that participants rolled after intoxication, there was a main effect of cannabis ($F_{1,23}$=5.05, p=0.035). Participants added less cannabis to their joints after smoking active cannabis (0.12 ± 0.03) compared to placebo cannabis (0.15 ± 0.02). There was no main effect of tobacco (placebo: 0.14 ± 0.03; active 0.13 ± 0.02) or interaction with tobacco.

[1] Skunk refers to high potency, indoor- grown floral material of unfertilized plants, whereby energy is diverted from seed production to cannabinoid synthesis ('sinsemilla'; meaning 'without seeds') (~15% THC) [32]
[2] Herbal cannabis refers to low potency – outdoor-grown imported floral material ('herbal', 'grass', 'weed') (~9% THC)[32]
[3] Hash refers to compressed blocks of plant matter ('resin', 'hashish') (~5% THC)[32]

In regards to the *actual dose of tobacco* participants rolled after intoxication, there was a main effect of cannabis ($F_{1,23}$=22.72, p<0.001). Participants added less tobacco to their joints after active cannabis (0.19 ± 0.03) compared to placebo cannabis (0.30 ± 0.03). There was no main effect of tobacco (placebo: 0.27 ± 0.03; active 0.23 ± 0.03) or interaction with tobacco.

There were no main effects or interactions for the *estimated dose of cannabis* (p's>0.05). However, there was a main effect of cannabis on the *estimated dose of tobacco* ($F_{1,23}$=6.99, p=0.014). After active cannabis (0.23 ± 0.04), participants correctly estimated they were using a smaller dose of tobacco than after placebo cannabis (0.36 ± 0.05). There was no main effect of tobacco (placebo: 0.31 ± 0.04; active 0.28 ± 0.04) or interaction with tobacco.

Table 5.1. Mean (SD), range and ratio (cannabis:tobacco) of the estimated amount and actual weight of cannabis and tobacco that participants rolled into a joint during the baseline session and after each drug condition.

		Cannabis in joint (g)		**Tobacco In Joint (g)**		**Ratio of cannabis to tobacco†**	
		Estimated	Actual	Estimated	Actual	Estimated	Actual
BASELINE	*Mean*	**0.28**	**0.14****	0.43	0.35	0.81:1	0.53:1
	SD	**0.23**	**0.12**	0.25	0.16	-	-
	Range	**0.02-0.90**	**0.00-0.44**	0.10-1.00	0.09-0.74	0.10:1 – 3.00:1	0.05:1 - 1.42:1
PLACEBO	*Mean*	**0.32**	**0.17****	0.38	0.33	1.12:1	0.63:1
	SD	**0.29**	**0.13**	0.26	0.17	-	-
	Range	**0.00-1.25**	**0.00-0.45**	0.00-1.00	0.00-0.74	0.05:1-3.50:1	0.05:1 – 2.00:1
TOB	*Mean*	**0.28**	**0.14***	0.34	0.27	1.22:1	0.54:1
	SD	**0.28**	**0.10**	0.26	0.12	-	-
	Range	**0.40-1.00**	**0.02-0.40**	0.00-0.90	0.00-0.46	0.11:1 – 4.00:1	0.11:1-1.74:1
CAN	*Mean*	**0.25**	**0.11*****	0.24	0.19	1.23:1	0.70:1
	SD	**0.20**	**0.12**	0.20	0.14	-	-
	Range	**0.00-0.70**	**0.00-0.41**	0.00-0.60	0.00-0.49	0.1:1 3.33:1	0.05:1 - 2.33:1
CAN+TOB	*Mean*	**0.32**	**0.12***	0.22	0.19	1.20:1	1.11:1
	SD	**0.49**	**0.19**	0.20	0.18	-	-
	Range	**0.00-2.00**	**0.00-0.59**	0.00-0.60	0.00-0.62	0.10:1 – 3.00-1	0.02:1-5.50:1

****p ≤ 0.001, **p ≤ 0.01, *p ≤ 0.05*

† N's range 17 - 24 as participants were excluded if they're response was 0 for either cannabis or tobacco (as a ratio cannot be calculated).

5.4 Discussion

This study examined estimated (self-report) and actual dose of cannabis and tobacco used in a joint. Recreational cannabis and tobacco users were assessed at baseline and after intoxication with cannabis and/or tobacco using a novel 'Roll a Joint' paradigm. I used a matched placebo-cannabis and rolling tobacco to create an ecological method where their weights, smell and appearance closely paralleled the active drugs.

Participants showed a 2-fold *over*estimation of the actual dose of cannabis they added to their joints, whilst accurately estimating the dose of tobacco. Importantly, this effect was replicated across all drug conditions. This suggests that overestimation of cannabis and accurate estimation of tobacco amounts is a reliable finding and was impervious to acute intoxication with cannabis or tobacco. These data, alongside other studies, suggest an equivalent downward titration either in the amount individuals rolled in joints (Freeman et al. 2014b) or the amount they inhaled (van der Pol et al. 2013). For example an Australian study which found participants overestimated the dose of cannabis to a similar degree, using a cannabis substitute (Norberg et al. 2012), suggests self-reported dose should be viewed with caution. One objective measure I would recommend is to implement this 'Roll a Joint' paradigm. Given the near equivalent overestimation found in the cannabis amount between these studies (Norberg et al. 2012), I suggest that use of a substitute, when placebo cannabis is not available, is adequate as long as a weight adjustment is made. I highly recommend that if users mix cannabis and tobacco, that those tobacco estimations are made with real tobacco and recorded, unlike in previous studies (Mariani et al. 2011; Norberg et al. 2012; Tomko et al. 2018; van der Pol et al. 2013).

I encourage investigators to utilise this methodology, however, precision in dose estimation remains a problem for other routes of administration as well and therefore further validation of dose estimation methods is required. Given the huge variation in popular cannabis routes of administration worldwide (see chapter 2), it would be

necessary to validate this method for other routes such as pipes, bongs and vaporizers. There is a stark difference between the methods by which people smoke cannabis in the UK, where this study was conducted, and where smoking a joint with tobacco is the most prevalent route, and the US where smoking cannabis through a blunt or pipe is common.

After smoking active cannabis, participants reduced both the amount of cannabis and tobacco they put into their joints compared to placebo cannabis, suggesting this paradigm is sensitive to acute satiety. Participants were only able to estimate they were using less tobacco *but not less cannabis*, which may imply they were aware of their satiety to tobacco, but not cannabis. This may be a consequence of the lack of information about cannabis due to illegal sales, which means a greater level of uncertainty regarding potency and the total weight of cannabis bought (e.g. an eighth of an ounce may not actually be what the user receives) especially for recreational users (Freeman et al. 2014b). Tobacco, however, is sold in standardised weights and is therefore potentially easier to estimate. Moreover, it is important to note that participants were still experiencing acute drug effects at the time of testing. Tobacco and cannabis differ in their appearance and typical dose per joint, which may have influenced accuracy; however, these factors were not manipulated and therefore are unlikely to account for the present results.

In the current turbulent climate of cannabis policy globally, finding accurate and standardised cannabis use metrics is essential to monitor levels of cannabis *and tobacco* consumption (Lynskey et al. 2016). There has certainly been some movement towards defining a standard cannabis unit (Casajuana Kogel et al. 2017; Wetherill et al. 2016) and certainly both frequency and quantity are important measurements (Zeisser et al. 2012). In Europe, the particular issue of smoking cannabis and tobacco is worrying and mostly disregarded (Broyd et al. 2016). Understanding how much cannabis is in a joint will inform important drug policy discussions (Ridgeway and Kilmer 2016) and

improve research outcomes when estimating dose, especially as self-reported use is often the main outcome variable used to link cannabis consumption to health outcomes. It is essential that dose be taken into account alongside potency measures. Here we find that users were unaware of how much cannabis they put in their joints, and are indeed *doubling the actual* amount. To our knowledge, this is the first study to show that both actual and estimated tobacco in joints is sensitive to acute cannabis administration indicative of cross-substance satiety. In order to investigate this further, use of smoking topography would be an essential next step (van der Pol et al. 2014).

5.4.1 Strengths and limitations

This study used a double-blind, placebo-controlled, four-way, crossover design with recreational users to investigate actual and estimated dose of cannabis and tobacco in a joint. A previous study found that recreational users have a poorer understanding of cannabis potency than heavy users (Freeman et al. 2014b) suggesting these findings cannot be extended to, and thus require replication with, heavier (dependent) users. Indeed, the precision of all dose measurement is still limited unless the potency of the cannabis is a known factor. Future research should aim to investigate dose and potency together. This research was conducted with a moderate number of recreational cannabis and tobacco users, and this may limit its generalizability (for example, to those who do not mix their cannabis with tobacco or to those who are dependent cannabis users). Further, this study was not designed to investigate sex differences, and therefore was not adequately powered to address this issue. At the same time, this 'Roll a Joint' paradigm has advantages over purely self-report measures of dose. We recognise this study did not have biologically verified abstinence or absorption; however, this is unlikely to influence our results as the residual cognitive effects of cannabis rarely last beyond 24 hours and should be minimal in infrequent users (Curran et al. 2002b; Curran et al. 2016). Finally, although participants in this study measured the amount of tobacco in their joints, the drug manipulation was on nicotine in tobacco,

and future research should improve upon this design to also understand the non-nicotinic components of tobacco.

5.4.2 Conclusions

Self-reported dose per joint is an inaccurate cannabis use metric. Here we report that a simple, novel and actionable ‘Roll a Joint’ paradigm can overcome these inaccuracies when collecting cannabis use metrics. Further, compared to placebo cannabis, active cannabis reduces the amount of both cannabis and tobacco rolled in a joint indicative of downward titration.

Interim Summary

> *"CBD is like THC's responsible twin. It looks out for you and makes sure you get home safely."* Jeremy Kossen, *VICE magazine (June 12th 2017)*

Thus far in this thesis, I have investigated the prevalence of cannabis and tobacco routes of administration utilising a large self-nominating sample and investigated the psychopharmacological interaction between the two drugs on memory, psychosis-like effects, reward processing and cannabis measurement, using the most popular route of administration (joint with tobacco) and a cannabis high in THC. For the next two chapters I would like to change track and investigate how cannabidiol (CBD), the non-intoxicating cannabinoid found in cannabis, might be used in a positive manner for individuals addicted to cigarettes. As reviewed in chapter 1, cannabinoids have been used in medicine for thousands of years. However, currently, cannabis is classified as a Schedule 1 drug according to the Misuse of Drugs Act (2001) as is therefore considered to have “no medicinal benefit”. Thus, despite its long history of recreational use in society, the understanding of medicinal aspects of cannabinoids is only in its infancy. CBD, until recently, was considered an unlicensed medication. There has been a recent move, parallel to the psychedelic renaissance, of using cannabinoids for treatment for a wide variety of disorders, with varying levels of quality of evidence and research to base conclusions upon. One of the areas that CBD may have promise is in the field of addiction. Therefore, these next two chapters report on research aiming to investigate the potential of CBD in nicotine withdrawal.

Chapter 6: Cannabidiol reverses attentional bias to cigarette cues in a human experimental model of tobacco withdrawal.

6.1 Introduction

Over 1.1 billion people smoke cigarettes worldwide (WHO, 2015). A primary addictive driver of cigarette smoking is nicotine withdrawal. Withdrawal occurs upon cessation of smoking and includes physiological symptoms (headache, nausea), affective symptoms (anxiety, depression and irritability) and impaired cognitive performance (delay discounting, response inhibition) (Grabski et al. 2016; Powell et al. 2010) 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 a major challenge in the treatment of addiction (Potenza et al. 2011). Current smoking cessation products help relieve withdrawal and craving, but even when using the currently most effective smoking cessation drug (varenicline), a majority (about 80%) still fail to maintain long-term abstinence (Schnoll and Lerman 2006). Smoking cessation medications may also have unpleasant side effects e.g. nausea associated with NRT (Cahill et al. 2016).

As reviewed in chapter 1, the eCB system is a neuromodulatory system that acts to maintain homeostasis in the brain by fine tuning other neurotransmitter systems. There is mounting evidence that the eCB system is involved in motivation for rewards including modulating the rewarding effects of drugs (Lawn et al. 2016; Parsons and Hurd 2015; Prud'homme et al. 2015; Viudez-Martinez et al. 2018; Zlebnik and Cheer 2016). In relation to nicotine dependence, cannabinoid receptor 1 (CB1R) antagonists, such as rimonabant, decrease nicotine conditioned place preference (CPP) and self-administration (SA) in preclinical models of nicotine addiction (Forget et al. 2005; Le Foll and Goldberg 2004). In human clinical trials, rimonabant increased smoking abstinence rates 1.6 fold (Cahill and Ussher 2011; Robinson et al. 2017). Although potentially effective, rimonabant was withdrawn from the market due to serious side-effects such as depression and suicidality.

Cannabidiol (CBD) is the second most abundant cannabinoid in cannabis. It has been shown to have broad therapeutic benefits (Pertwee 2008; Russo 2016) and is showing initial promise as a treatment for addiction, anxiety and schizophrenia. The psychological properties of CBD are suggestive of a potential drug for smoking cessation. These include its lack of intoxicating and subjective effects (Babalonis et al. 2016; Haney et al. 2015; Hindocha et al. 2015a) alongside its anxiolytic (Bergamaschi et al. 2011; Fusar-Poli et al. 2009) effects in humans. Its anxiolytic properties are particularly relevant as anxiety is a primary symptom of tobacco withdrawal (Hughes 1992). CBD is likely to be anxiolytic because it activates 5HT1a serotonergic receptors (Russo 2016; Russo et al. 2005).

The first human pilot study to investigate CBD as a treatment for nicotine dependence randomised participants to either one-week of ad-hoc CBD (65% bioavailability) or placebo inhaler to be used when participants had the urge to smoke. CBD reduced the number of cigarettes participants reported that they smoked by almost 40% however, it did not affect craving for cigarettes (Morgan et al. 2013a). No neurocognitive mechanisms through which CBD may assist with the treatment of smoking cessation were investigated. On the basis of previous findings (Morgan et al. 2010a), the authors proposed a reduction in the salience of drug cues could be one candidate mechanism.

Attentional bias (defined in section 1.2.7.3.2) is a potentially important in-laboratory predictive marker of the salience of drug cues. As indexed by dot-probe tasks, it is heightened during acute abstinence (Grabski et al. 2016); predicts short-term relapse; (Waters et al. 2003) and is thought to play a causal role in maintaining addiction (Franken 2003). Attentional bias to tobacco stimuli at a short (compared to longer) exposure interval is particularly important as tobacco abstainers show greater bias to these cues only at short exposure (Freeman et al. 2012a). CBD may reduce the salience of smoking cues which would be consistent with preclinical and human experimental and neuroimaging research.

To investigate this possibility, I designed a study to investigate the following question: What are the effects of CBD on tobacco withdrawal, craving and attentional bias after overnight abstinence? This is the first study to investigate the effects of CBD during nicotine withdrawal in humans. I employ 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 facilitate translational research. Specifically, I hypothesised that: (1) overnight nicotine abstinence, compared with satiety, will produce a range of nicotine withdrawal symptoms in dependent cigarette smokers which include greater attentional bias (at the short stimulus exposure), higher pleasantness of cigarette-related stimuli and increased craving and withdrawal; (2) CBD in comparison to placebo, would attenuate attentional bias and pleasantness of cigarette-related stimuli, craving and withdrawal symptomology relative to pre-drug scores; (3) CBD in comparison to placebo, will not produce any significant cardiovascular or side effects.

6.2 Method

6.2.1 Design and participants

Thirty participants attended 3 sessions (mean: 7.85, standard deviation: 2.77) days between sessions) – see figure 6.1. Participants smoked as normal before their first (baseline) session, verified with expired Carbon Monoxide (CO) ≥ 10 ppm (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 used to compare the effects of 800mg oral CBD with matched placebo (PBO) after overnight smoking abstinence. Treatment order for abstinent sessions was randomised and counterbalanced. Participants received the drug based on a randomisation code, which was balanced for gender (www.random.org). This code was concealed from experimenters until all data was

collected and entered. Drug concealment occurred through participant-numbered, opaque, sealed envelopes. There was a minimum washout of 1-week between drug sessions to preclude potential CBD carry-over effects following previous research (Babalonis et al. 2016; Haney et al. 2015).

Dependent cigarette smokers were recruited from the community 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) Fagerström Test for Nicotine Dependence (FTND) score ≥ 4 (moderate dependence) (Heatherton et al. 1991); iv) smoking first cigarette of the day within an hour of waking; iv) negative drug urine screen for all major drugs of abuse at baseline. Exclusion criteria were: i) use of nicotine replacement therapy/cessation 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 breastfeeding; vi) allergies to CBD, gelatine, lactose, microcrystalline cellulose or chocolate.

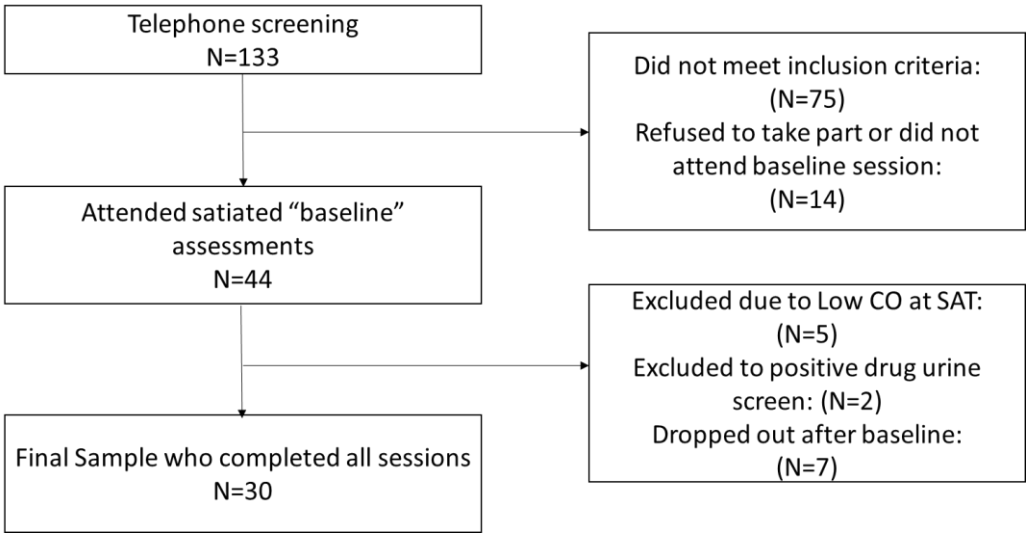


Figure 6.1. Participant recruitment diagram. The final sample included 30 participants who completed all three sessions

6.2.2 Power calculation

I calculated that N=20 would be necessary to have power of 95% at an alpha of 5% 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 (23.25 cigarettes) in Morgan et al. (2013; 29). This sample size was increased by 50% yielding a final sample of 30 to adjust for “winner’s curse” (Button et al. 2013) i.e. over-inflation of effect sizes from initial positive studies.

6.2.3 Drug administration

Participants were administered 800mg oral CBD doses (pure synthetic (-)-CBD, STI Pharmaceuticals, Essex, England) or matched placebo (lactose powder) in matched capsules in a double-blind, counterbalanced manner. The 800mg CBD is well tolerated, shows no abuse liability, does not modify the reinforcing properties of smoked cannabis (Babalonis et al. 2016; Haney et al. 2015) or exacerbate the adverse effects of fentanyl (Manini et al. 2015). 800mg per day for three days has been shown to reduce anxiety and cue induced craving in individuals addicted to opiates who had been abstinent for a week (Hurd et al. 2015). 800mg dose was chosen as it has shown clinical efficacy for schizophrenia (Leweke et al. 2012). 600mg has been shown to influence neural networks that include medial temporal, prefrontal and striatum brain regions therefore 800mg should have a similar effect (Bhattacharyya et al. 2015). This 800mg dose produces an increase in plasma concentrations after administration (Cmax = 77.9 ±25 ng/mL, Tmax=180 minutes) (Babalonis et al. 2016; Haney et al. 2015). The oral route of administration was chosen in rather than inhaled because data on plasma concentrations were available. Furthermore, there is far higher levels of variability with the inhaled route which is dependent on how much is exhaled, breath holding protocols and bioavailability, the latter is not yet reported (Solowij et al. 2014). Finally, CBD, when vaporised can be irritating for the throat which generates a cough (Solowij et al. 2014).

6.2.4 Assessments

6.2.4.1 Visual probe task (Figure 6.2)

This task was implemented as a measure of attentional bias (Charles et al. 2015). Thirty tobacco smoking (target) and composition-matched neutral (non-target) images were

shown (Mogg et al. 2003). 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 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 as quickly and accurately as possible (defined as a "correct trial" if a correct response was made). Probes replaced the cigarette-related and neutral images equally often. The position of image type, probe location, and stimulus duration was 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).

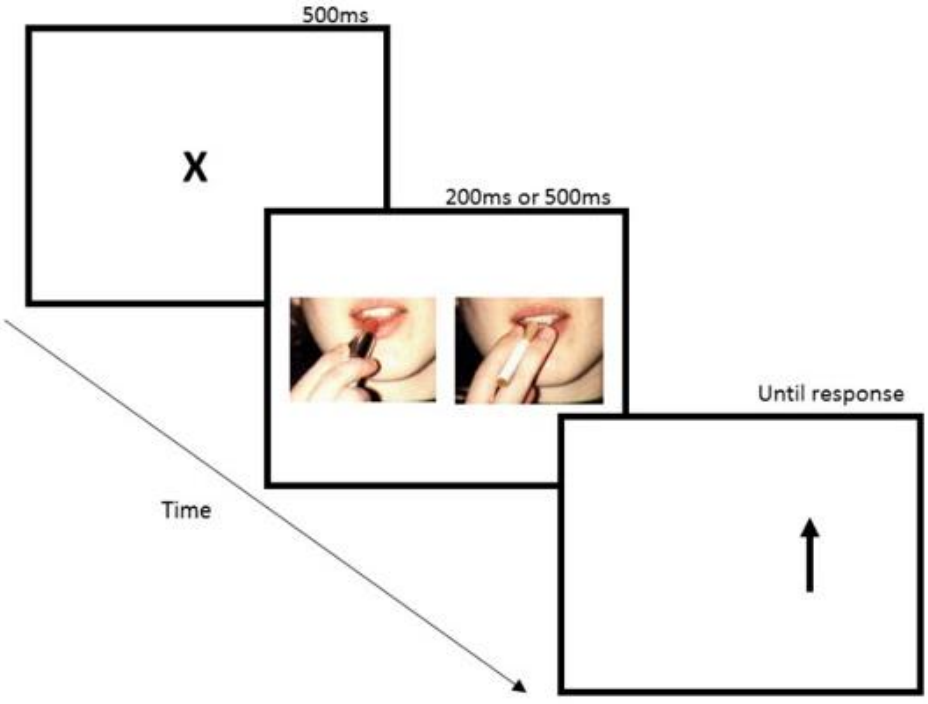


Figure 6.2. Trial structure for the visual probe task. Example of cigarette (right) and matched neutral stimuli (left) provided.

6.2.4.2 Pleasantness Rating Task (PRT)

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. Cigarette stimuli involved smoking-related scenes and were the same as those in the visual probe. Participants rated the pleasantness of each image on a scale of -3 (very unpleasant) to +3 (very pleasant). Valence was recorded. Three versions were available for counterbalancing. The experiment was conducted using Psychopy (Peirce 2007; 2009). A variant of this task was also utilised in Chapter 4.

6.2.4.3 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 with items: “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 on a 10-point VAS from “not at all” to “extremely”.

6.2.4.4 Trait Questionnaires

The FTND was used to assess nicotine dependence (Heatherton et al. 1991). Anxiety was assessed with the Trait Anxiety Inventory (STAI) (Spielberger et al. 1970) and depression with the Beck Depression Inventory (BDI) (Beck et al. 1961). A comprehensive drug history was taken (Hindocha et al. 2017). Premorbid verbal intelligence was indexed by the Spot The Word task (Baddeley et al. 1993).

6.2.5 Procedure

After telephone screening, eligible participants attended a baseline ‘satiated session’ prior to which they smoked as normal. This involved further screening assessments (CO, 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) after they were deemed eligible (T1; +12 mins), were asked to smoke a cigarette (Marlboro Gold) to ensure satiety (+30 mins), then completed a second measure of craving and withdrawal (T2; + 35 mins), the visual probe task (+ 60 mins), PRT (+68 mins) and a final measure of craving and withdrawal (T3; +75 mins). 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 and cardiovascular measures (QSU-B, MPSS, HR, BP (T1, +5 mins)). CBD or matched placebo was then orally administered (+10 mins). After drug administration, participants completed half the trait questionnaires in each session. At 70 mins (T2) and 130 (T3) minutes they again completed the MPSS, QSU-B, HR and BP. Participants then completed the visual probe (+180 mins) and PRT (+188 mins). At 200 minutes, participants completed a final measure of craving and withdrawal (T4). Timing of assessments was in line with peak drug effect (section 6.2.3) A detailed schedule of assessments can be found in *Table 6.1.* All participants provided written informed consent. Ethical approval was given by UCL Ethics Committee (Appendix C). Participants were reimbursed £10/hour.

Table 6.1. Schedule of assessments on the satiated and abstinent sessions.

SATIATED (SAT)		**ABSTINENT ABST)**	
TIME		**TIME**	
0	Arrival	**0**	Arrival
12	MPSS QSU [1]	**5**	MPSS QSU HR BP [1]
30	Cigarette	**10**	Drug administration
35	MPSS QSU [2]	**70**	MPSS QSU HR BP [2]
60	Visual Probe	**130**	MPSS QSU HR BP [3]
68	PRT	**190**	Visual Probe
75	MPSS QSU [3]	**198**	PRT
-	-	**200**	MPSS QSU [4]

6.2.6 Statistical analysis

Statistical analyses were performed in the Statistical Package for Social Scientists (SPSS 24; IBM, Chicago, IL). Visual inspection of diagnostic plots was used to check for normality. Where the assumption of sphericity was violated, the Greenhouse-Geisser correction was used and rounded to the nearest integer. η^2p denotes partial eta-squared. Outliers > 1.5 x the interquartile range (IQR) were winsorized to the next highest/lowest value. For the PRT, 4.2% of the data were missing due to technical issues and were replaced with the means of the condition. Sensitivity analysis showed that winsorization or mean imputation did not modify any result.

Only correct trials (99.97% of the data) were analysed for the visual probe and 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. 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 visual probe task; and as cigarette_valence – neutral_valence for the PRT.

The visual probe and PRT 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. For the visual probe task, an additional task-specific factor of 'exposure time' was included to investigate automatic (short) in comparison to strategic (long) processing. Interactions between condition and exposure were explored via pair-wise post-hoc comparisons, Bonferroni-corrected locally within each omnibus term.

Craving (QSU) and withdrawal (MPSS) symptomology were analysed with two repeated measures ANOVA because of the difference in timings and number of assessments of craving and withdrawal. The first investigated SAT (T2 – immediately

after a cigarette) vs. abstinence (T1 - pre-drug administration). The second compared CBD in comparison to PBO across all time points (T1(pre-drug), T2, T3, T4). Interactions between condition and time were assessed with post-hoc comparisons, Bonferroni-corrected locally within each omnibus term.

Side-effects, HR and BP were measured three times on abstinent sessions, therefore these data were analysed with a 2 (CBD, PBO) x 3 (T1 (pre-drug), T2, T3) ANOVA. Interactions between condition and time were assessed with post-hoc comparisons, Bonferroni-corrected locally within each omnibus term.

Scaled Jeffreys-Zellner-Siow (JZS) Bayes Factors (BF) were calculated when the main effect of drug (CBD vs. PBO) was not significant according to frequentist statistics (p>0.05). I used a scaled-information prior of r = 1 (Rouder et al. 2009).

Carry-over effects were assessed using an additional between-subjects factor of "order". No order effects were found for the main analyses (as evidenced by no interactions or main effects involving treatment order). Therefore, I report results without accounting for order. As I did not have any specific *a priori* hypotheses regarding covariates, I did not include any as per Kraemer (2015).

6.3 Results

6.3.1 Participant characteristics

30 participants (14 female) took part. The sample had a mean (SD) age of 28.07 (8.66) years old, with an FTND score of 5.56 (1.13) demonstrating moderate dependence (Heatherton et al. 1991). They smoked 13.5 (2.39) cigarettes per day, which is slightly more than the national adult average of 11.5 (NHS 2016). Further demographics, trait scores and cigarette smoking information can be found in Table 6.2. Use of other drugs was minimal in this population (Table 6.3).

Table 6.2. Participants' demographic and trait variables. Results are displayed as mean (SD).

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)	25.5 (15.87)
YEARS SMOKED	9.55 (7.36)
YEARS SMOKING >10+ CIGARETTES/DAY	8.17 (7.08)
LIFETIME QUIT ATTEMPTS (N=25)	3.2 (3.91)
MOST SUCCESSFUL QUIT ATTEMPT (DAYS)	100.48 (163.47)
BODY MASS INDEX	23.98 (7.78)
SPOT THE WORD	48.03 (4.15)
STAI	40.53 (9.4)
BDI	10.36 (7.54)

Table 6.3. Drug use history (N = the number of people who used the drug in the past year). Results are displayed as mean (SD).

	ALCOHOL	**CANNABIS**	**MDMA**	**COCAINE**
N	26	17	9	9
DAYS SINCE LAST USE	6.39 (10.13)	100 (68.30)	84.66 (82.22)	100 (56.12)
NUMBER OF 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)
TYPICAL AMOUNT PER SESSION	7.1 units (3.23)	0.87 joints (0.69)	258.33mg (144.70)	800mg (0.83)

6.3.2 Manipulation/abstinence checks

6.3.2.1 Time since last smoked

There was a significant main effect of abstinence ($F(1,29)= 3289.03$, $p<.001$, $\eta^2p =.99$) where on the satiated session, participants last smoked M: 0.41 (SD: 0.40) hours previously, in comparison to abstinent. There was no main effect of drug ($F(1,29)=0.18$, $p=.675$, $\eta^2p=.006$). Participants last smoked M: 10.97 (SD:0.96) hours previously on

the CBD session and M:11.03 (SD:0.95) on the PBO session. Thus time since last smoked verified abstinence.

6.3.2.2 CO

There was a significant main effect of abstinence ($F(1,29)= 167.83$ $p<.001$, $\eta^2p=.84$) which shows CO was higher in the satiated condition (M: 17.73 ppm SD: 6.63) than in the abstinent conditions. There was no main effect of drug ($F(1,29)=6.13$, $p=.019$, $\eta^2p=.17$) where CO was 4.27ppm (SD:2.23) for CBD and 4.17 (SD:2.69) for PBO. Thus abstinence was biologically verified.

6.3.3 Attentional Bias

6.3.3.1 Visual probe task (Fig 6.3)

There was a main effect of abstinence ($F(1,29)=9.52$, $p=.004$, $\eta^2p=.27$) 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 ($F(2,58)=4.66$, $p=.013$, $\eta^2p=.14$). The interaction showed that under the short stimulus exposure, there was greater attentional bias to cigarette cues in the PBO condition, in comparison to SAT (45.15ms (95% CI: 71.77, 18.54), $p=.001$, d: .789), as well as greater attentional bias in the PBO condition in comparison to CBD (36.47ms (95% CI: 64.18, 8.77), $p=.007$, $d=.704$) but not between SAT and CBD (-8.68ms (95% CI: -28.43, 11.07), $p=.82$). Under the long stimulus exposure, none of these comparisons were significant. Additionally, AB was greater to cigarette cues under the long, in comparison to short, exposure time for CBD (20.94ms (95% CI: 40.29, 5.15), $p=.015$) but not under SAT ($p=.263$) or PBO ($p=.155$). There was no main effect of exposure time ($F(1,29)=2.14$, $p=.155$, $\eta^2p=.07$).

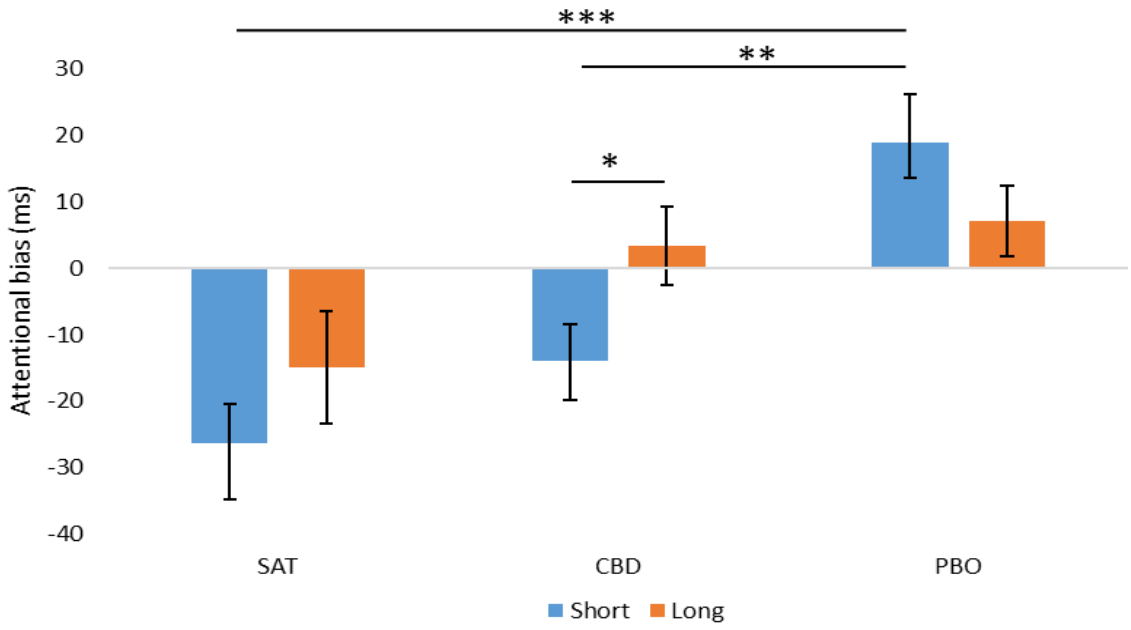


*Figure 6.3. Attentional bias across satiated (30 mins post-cigarette) and abstinent (180 mins post-drug administration) for both short and long exposure times. Estimated marginal means are presented with 95% CI error bars. * p≤ .05, ** p≤ .01, *** p≤ .001*

6.3.4 Pleasantness Rating Task

6.3.4.1 Valence (Fig 6.4)

There was no main effect of abstinence ($F(1,29)=0.53$, $p=.47$, $\eta^2p=.02$). There was a significant main effect of drug ($F(1,29)=7.41$, $p=.011$, $\eta^2p=.20$), indicating less valence bias towards cigarette stimuli on CBD compared to PBO (-0.51 (95% CI: -0.99, -0.03); $d=.514$).

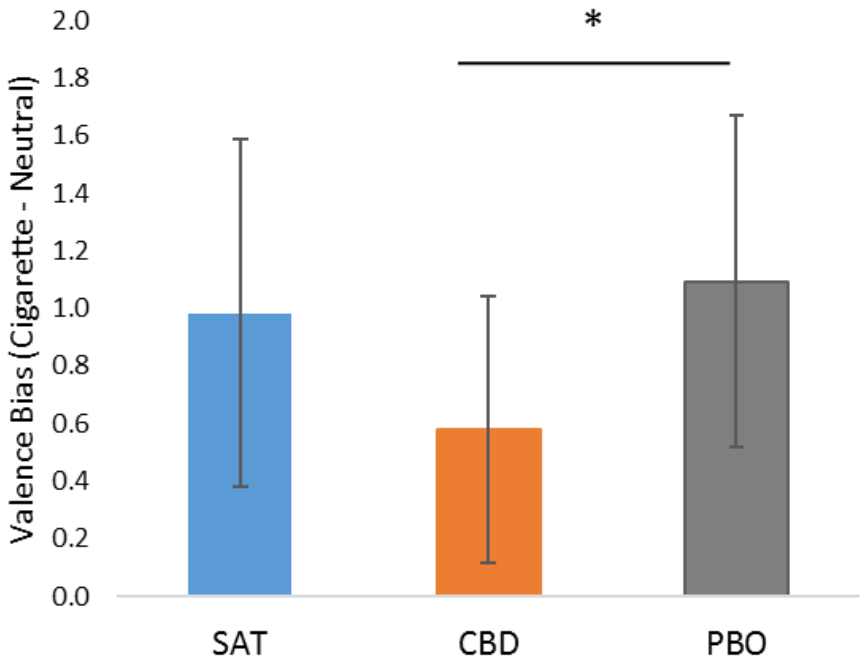


*Figure 6.4. a) Bias in pleasantness rating (calculated as cigarette valence minus neutral valence) for satiated (38 mins post-cigarette) and abstinent (188 mins post- drug administration) conditions. Estimated marginal means are presented with 95% CI error bars. * p≤ .05, ** p≤ .01, *** p≤ .001.*

6.3.5 Craving (Fig 6.5)

Pre-drug QSU scores were greater in abstinent conditions versus satiation ($F(1,29)=99.75$, $p<.001$, $\eta^2p=.78$). There was no difference between CBD and PBO, pre-drug administration ($p=.99$) confirmed by a Bayesian analysis showing the null was 7.08 more likely than the alternative given the data (JZS BF: 7.08). To investigate if CBD attenuated craving in comparison to placebo on abstinent sessions, I conducted an ANOVA that showed a main effect of time ($F(2,54)=8.34$, $p<.001$ $\eta^2p=.22$), however there was no main effect of drug ($p=.81$) confirmed by a Bayesian analysis (JZS BF=6.87), or drug x time interaction suggesting no difference between CBD and PBO.

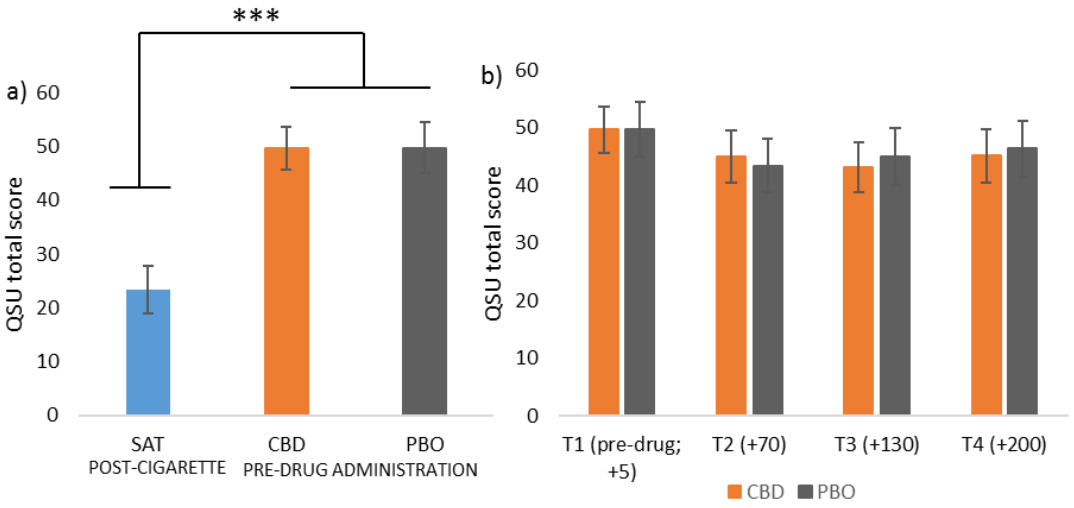


*Figure 6.5. Scores for the QSU-B (craving). Left panel (a) shows significantly greater craving on abstinent sessions before drug administration, in comparison to satiation scores after a cigarette. Right panel (b) compares CBD and PBO across all time points pre- and post- drug administration (T2 onwards). See table 6.2 for details on timing. Estimated marginal means with 95% CI are presented. * p≤ .05, ** p≤ .01, *** p≤ .001.*

6.3.6 Withdrawal (Fig 6.6)

6.3.6.1 MPSS total

Pre-drug MPSS scores was greater under abstinent conditions versus satiation (F(1,29)=29.88, p<.001, η^2p=.51) suggesting abstinence increased withdrawal. There was no difference between CBD and PBO, pre-drug administration (p=.85) confirmed by Bayesian analysis showing the null was 6.95 more likely than the alternative given the data (JZS BF: 6.95). To investigate if CBD attenuated withdrawal in comparison to placebo on abstinent sessions, I conducted an ANOVA that showed a main effect of time (F(2,69)=8.98, p<.001, η^2p=.24) however there was no effect of drug (F(1,29)=.22, p=.64 η^2p=.01) confirmed by a Bayesian analysis (JZS BF= 6.35), or drug x time interaction.

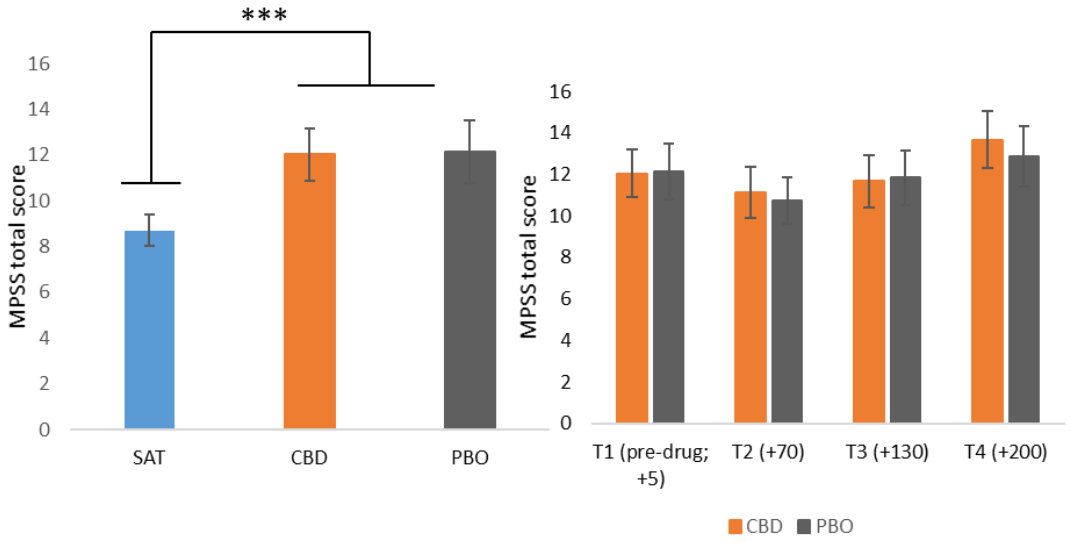


*Figure 6.6. Scores for the MPSS (withdrawal symptoms). Left panel (a) shows significantly greater withdrawal on abstinent sessions before drug administration, in comparison to satiation scores after a cigarette. Right panel (b) compares CBD and PBO across all time points pre- and post- drug administration (T2 onwards). See table 6.2 for details on timing. Estimated marginal means with 95% CI are presented. * p≤ .05, ** p≤ .01, *** p≤ .001.*

6.3.6.2 Amount of time spent with urge to smoke

Pre-drug time spent with urges was significantly greater under abstinent than satiated sessions $F(1,29)=27.96$, $p<.001$, $\eta^2p=.49$ suggesting abstinence increased the amount of time spent with urges to smoke. There was no different between CBD and PBO, pre-drug administration ($p=0.536$; JZS BF in support of the null= 5.86). To investigate if CBD attenuated craving in comparison to placebo on abstinent sessions, I conducted an ANOVA that showed a main effect of time ($F(3,87)=8.65$, $p<.001$, $\eta^2p=.23$) which showed that time spent with urges decreased from T1 (3.17, 95% CI 2.79-3.64) to T3 (2.40, 95% CI 1.97-2.82), and increased from T3 to T4 (2.80, 95% CI 2.38-3.22). However there was no effect of drug ($p=1.00$; JZS BF in support of the null= 7.08) There was no drug x time interaction $F(2, 68)=.25$, $p=.81$, $\eta^2p=0.00$).

6.3.6.3 Strength of urges to smoke

Pre-drug strength of urges was significantly greater under abstinent than satiated sessions $F(1,29)=26.26$, $p<.001$, $\eta^2p=.48$ suggesting abstinence increased the strength

of urges. There was no different between CBD and PBO, pre drug administration (p=0.879; JZS BF in support of the null= 6.99). To investigate if CBD attenuated craving in comparison to placebo on abstinent sessions, I conducted an ANOVA that showed a main effect of time (F(3,87)=4.33, p=.007, η^2p=.13) which showed that time spent with urges decreased significantly from T1 (2.92, 95% CI 2.58-3.25) to T2 (2.40, 95% CI 2.02-2.78), and increased from T2 to T3 (2.48, 95% CI 2.10-2.87) and T4 (2.73, 95% CI 2.31-3.16). However there was no effect of drug (p=.61; JZS BF in support of the null= 6.20) There was no drug x time interaction F(3, 87)=0.65, p=0.58, η^2p=0.02).

6.3.7 Cardiovascular effects

6.3.7.1 Heart rate (HR)

There was a main effect of time (F(1,39)=33.73, p<.001, η^2p=.54) which showed HR decreased over time. There was no main effect of drug (p=.30) confirmed by a Bayesian analysis (JZS BF= 4.17) and no interaction between drug and time.

6.3.7.2 Blood pressure (BP)

A main effect of drug (F(1,29)=6.72, p=.015, η^2p=.19), showed higher systolic BP after PBO than after CBD (+3.40, 95% CI 0.72 – 6.08). There was a main effect of time (F(2,58)=13.24, p<.001, η^2p=.31) which showed that systolic BP decreased over time. There were no main effects or interactions for diastolic BP.

6.3.8 Side-effects

Strong Drug effect: There was no main effect of drug (F(1,29)=.80, p=.379, η^2p=.03) confirmed by Bayesian analysis (JZS BF: 4.82), time (F(2,58)=.37 p=.695, η^2p =.01), or drug x time interaction (F(2,58)=2.18, p=.123, η^2p=.07).

Good Drug effect: There was no main effect of drug (F(1,29)=.10, p=.922, η^2p=.00) confirmed by Bayesian analysis (JZS BF:7.04), time (F(2,58)=2.76, p=.072, η^2p =.09), or drug x time interaction (F(2,58)=2.18, p=.123, η^2p =.07).

Willing to take drug again: There was no main effect of drug (F(1,29)=2.35, p=.136, η^2p=.08) confirmed by Bayesian analysis (JZS BF: 2.35), time (F(2,58)=0.42, p=.661, η^2p=.01), or drug x time interaction (F(2,58)=1.12, p=.306, η^2p=.040).

Like drug effect: There was no main effect of drug (F(1,29)=.01, p=.947, η^2p=.00) confirmed by Bayesian analysis (JZS BF: 7.06) or drug x time interaction (F(2,58)=.03, p=.968, η^2p=.00). There was a main effect of time (F(2,58)=3.53, p=.036, η^2p=.11) which showed liking decreased over time.

I have a stomach ache: There was no main effect of drug (F(1,29)=.00, p=.957, η^2p=.00) confirmed by Bayesian analysis (JZS BF:7.07), time (F(2,58)=.01, p=.988, ηp^2=.000), or drug x time interaction (F(2,58)=1.44, p=.245, η^2p=.05).

I have a headache: There was a drug x time interaction (F(2,58)=3.17, p=.049, η^2p=.099). Exploration of the interaction showed no significant pairwise comparisons. There was no main effect of drug (F(1,29)=.04, p=.839, η^2p=.00) confirmed by Bayesian analysis (JZS BF:6.93), or time (F(2,58)=.80, p=.456, η^2p=.03).

6.4 Discussion

This study employed an experimental medicine approach to investigate the effects of a single 800mg oral dose of CBD on nicotine withdrawal. I found evidence that compared to placebo; CBD reversed the attentional bias to cigarette cues in abstinent and dependent cigarette smokers such that it was no longer significantly different from attentional bias when they were satiated. Simultaneously, I observed a reduction in explicit pleasantness, sometimes referred to as “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 of craving and withdrawal between CBD and placebo. This suggests 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. 2010a) and preclinical research (Ren et al. 2009). Moreover, no significant side effects were

observed. These results therefore support the potential of CBD in targeting specific neurocognitive processes in nicotine addiction.

To be specific, 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 participants in this study, on average, were over 40ms faster to detect probes replacing smoking (vs. neutral) cues under placebo than under CBD. This was observed in the short exposure time only, consistent with our initial hypothesis and with previous findings regarding attentional bias (Freeman et al. 2012a) and CBD (Morgan et al. 2010a). The short exposure time is related to *implicit* automatic processing and initial orientation to cues, which occur outside the individual's explicit awareness (Field and Cox 2008; Freeman et al. 2012a).

These results suggest that one potential candidate mechanism by which CBD may exert anti-addictive effects is by normalising the salience of drug cues. This in line with the incentive salience model of drug addiction (Robinson and Berridge 2001) and IRISA model (Goldstein and Volkow 2011). 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. However, clearly attentional bias is the only driver of nicotine addiction, and other mechanisms require investigation.

As well as effects of CBD on implicit attentional bias, a reduction in explicit pleasantness for cigarettes under CBD compared to placebo was observed. Explicit pleasantness is important in regards to addiction because it partly indexes the reinforcing value of a drug. In humans, users of high, in comparison to low, CBD: THC ratio cannabis showed lower self-reported pleasantness of cannabis stimuli which follows the same pattern as the present study (Morgan et al. 2010a) and may be related to endocannabinoid involvement in hedonic experiences and reward responsivity (Mahler et al. 2007). However, there was no difference between abstinence and satiated sessions, which

was unexpected as it was hypothesised as it had previously been shown (Field et al. 2004).

The absence of CBD effects on withdrawal and craving are surprising because theoretically, the incentive salience model of Robinson and Berridge would suggest a reduction in attentional bias would be accompanied by a reduction in craving. Moreover, Hurd et al. (2015) found that CBD reduced *cue-induced craving* and anxiety which was maintained for 24 hours in heroin users (however a different paradigm was used). It is notable that both Morgan et al. (2013a) and the present study did not find effects on tonic craving, therefore CBD may not be effective for all smokers but only those experiencing heightened attentional bias to drug cues. The incentive salience hypothesis equates craving with wanting a drug but not liking a drug, and argues further that craving reflects the attribution of intense motivation for reward-associated stimuli. In the present research, CBD reduced attentional bias, arguably an index of incentive salience, but had no impact on craving. Given that craving and attentional bias are dissociated here, with CBD specifically attenuating attentional bias, this research seems to be inconsistent with the model. It may be that the observed reduction in attentional bias is a result of a general motivational effect in that CBD may be reducing general orienting to salient cues. Future research should investigate whether CBD also modifies orienting to other salient cues such as food cues. This has been investigated in street cannabis where individuals smoking cannabis high (in comparison to low) in CBD had significantly lower attentional bias to both cannabis and food-related cues (Morgan et al. 2010a).

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. 2013a; Scherma et al. 2008). Here, I was unable to measure anandamide levels, because these can only be assessed with the collection of cerebrospinal fluid, which involves an invasive medical procedure (lumbar puncture). 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).

6.4.1 Strengths and Limitations

Firstly, I used an experimental medicine approach to investigate mechanistic effects of single dose CBD during overnight tobacco withdrawal therefore it is unclear whether these effects will translate to the clinic and how long they might last. The visual probe task only provides a cross-sectional snapshot of attentional bias in a laboratory setting and may suffer from low internal reliability (Ataya et al. 2012). In this case, Ecological Momentary Assessment may be more indicative of attentional bias in actual drug taking environments. Additionally, use of eye tracking, fMRI or EEG would provide 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 repeated dosing using a range of doses (Zuardi et al. 2017). Finally, compliance with tobacco smoking abstinence instructions was verified with breath CO but abstinence from other nicotine products was based on self-report, therefore I could not objectively verify that participants had not used other nicotine products. However, craving and withdrawal scores were markedly higher under abstinence than satiation suggesting self-report was reliable.

6.4.2 Conclusions

This is the first study to investigate effects of CBD on nicotine withdrawal. After overnight tobacco abstinence, cigarette smokers administered 800mg CBD, in comparison to placebo, show a reduced salience of cigarette cues and reduced pleasantness 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 specific neurocognitive components of tobacco use disorder and suggests that one potential mechanism by which CBD may exert its effects on addiction is via a reduction in the salience of drug cues. These results support the growing literature regarding CBD in the treatment of addictive disorders.

Chapter 7: The effects of cannabidiol on impulsivity and memory during abstinence in cigarette dependent smokers

7.1 Introduction

Nicotine withdrawal consists of multiple physiological, affective and cognitive symptoms that can peak within hours of stopping smoking (Brown et al. 2013; Hughes 2007; Shiffman et al. 2002). Grabski et al. (2016) recently conducted a meta-analysis of cognitive tasks sensitive to tobacco abstinence (see section 1.2.4.1). Abstinent smokers, in comparison to satiated smokers, show greater impulsivity on two specific impulsivity tasks: *delay discounting* and *response inhibition.* Delay discounting is defined as the degree to which one prefers smaller, more immediate rewards over larger, more delayed rewards (Bickel et al. 2014a). *Response inhibition* is defined as the ability to stop a pre-potent response e.g. craving for cigarettes; it is a marker of executive functioning; and theoretically important for successful smoking cessation (De Wit 2009)). These tasks assess impulsive decision making and impulsive action, respectively. Grabski et al (2016) found that abstinent smokers also showed impaired arithmetic and recognition memory ability, both of which includes a core component of working memory and were therefore interpreted as potential evidence for effects of abstinence on working memory (Mendrek et al. 2006; Xu et al. 2005). Therefore, pharmacotherapies which aim to improve cognition, such as memory and impulsivity, during tobacco abstinence may be useful for the treatment of tobacco use disorders.

Cannabidiol (CBD), the non-intoxicating cannabinoid found in cannabis, may have a novel application in nicotine withdrawal (see chapter 6). Thus far, CBD has been shown to reduce craving in both pre-clinical and clinical models of heroin addiction (Hurd et al. 2015; Ren et al. 2009). Furthermore, it may have a specific utility in cigarette smoking. Morgan et al. (2013a) found that a single week of ad-hoc CBD via inhaler, compared to placebo, reduced the number of self-reported cigarettes smoked by almost 40%, however craving was unaffected. In chapter 6, I found that 800mg oral CBD, in comparison to placebo, reversed attentional bias away cigarette cues, and reduced explicit liking of cigarette stimuli but also in the absence of changes in withdrawal and craving. CBD may also have pro-cognitive effects and has, in multiple studies, been

shown to protect against the detrimental cognitive effects of THC, and particularly in the domains of verbal episodic and recognition memory (Englund et al. 2013; Morgan et al. 2012; Morgan et al. 2010b; Osborne et al. 2017). In regards to impulsivity, Bhattacharyya et al. (2010) found opposite effects of THC and CBD on the BOLD response, in the para-hippocampal gyrus during a response inhibition task. Borgwardt et al. (2008) found CBD reduced the left temporal cortex and insula but was not associated with increases in regional activity relative to placebo. Finally, no research has investigated the effects of CBD on delayed discounting.

Experimental medicine approaches to study tobacco abstinence are cost-effective and mechanistic evaluations of a medication, and may facilitate drug discovery (Lerman et al. 2007). This chapter specifically aimed to answer the following question: What are the effects of CBD in comparison to placebo on attenuation of the cognitive effects of nicotine abstinence? I hypothesised that after overnight cigarette abstinence in dependent cigarettes smokers, CBD would improve performance in working and verbal episodic memory and on impulsivity tasks, in comparison to placebo.

7.2 Methods

7.2.1 Design and participants

As described in section 6.2.1

7.2.2 Power calculation

As described in section 6.2.2

7.2.3 Drug administration

As described in section 6.2.3

7.2.4 Assessments

7.2.4.1 Delay discounting task (Field et al. 2006)

In this task, participants had to make 91 alternative forced 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 (e.g. “Which would you prefer: £100 in 180 days or £30 now?”). The indifference parameter (k), which was the main variable of interest was derived from the indifference points from each session and calculated according to Reed et al. (2012). This is defined as the point where an individual switches from larger later rewards to smaller sooner rewards. It is an estimation of the subjective value of the larger later reward. When this value is replicated over numerous delay values, the indifference point represents an individual’s preference for reward over time (Madden and Johnson 2010).

7.2.4.2 Go/no-go task (Logan et al. 1997)

This task required participants to make a response when a designated “go” cue (Star) was presented and withhold responding to a designated “no-go” cue (Arrow). Each trial began with a fixation cross displayed for 500 ms. The cues were shapes presented in the center of a screen for 1000 ms. A practice phase of 6 trials was implemented, where participants received feedback on their performance. The first 20 trials were go-trials to build a pre-potent response and the remaining 90 trials were made up of 30 no-go trials and 60 go-trials, presented in randomized order. The main variable of interest was the commission errors (i.e. a response made on NoGo trials).

7.2.4.3 Prose recall

The Prose Recall subtest of the Rivermead Behavioral Memory Test (Wilson et al. 1991) taps episodic memory. Participants heard a 30s passage of prose (a news bulletin) and recalled its contents immediately and after a delay of 25 minutes. The

primary outcome is the mean number of idea units recalled. Three versions were presented in a counterbalanced order across each of the three sessions.

7.2.4.4 N back

See section 3.7.2.2.2 for a full description. This was used to provide a measure of working memory, as well as maintenance and manipulation of information.

7.2.5 Procedure

Participants were instructed to remain abstinent from midnight the night before each of the two experimental 'abstinent' sessions resulting in an average of 11 hours abstinence (range 9.5-13 hours). Each abstinent session began with confirmation of cigarette abstinence (breath CO) and assessment of craving (measured by the Questionnaire of Smoking Urges-Brief (Toll et al. 2006) and withdrawal (measured by the Mood and Physical Symptoms Scale (West and Hajek 2004)), these data are reported in chapter 6. Next, drug administration took place. Trait questionnaires were conducted immediately after this and were equally split between the two abstinent sessions. Testing began 150 minutes after drug administration so CBD would reach peak levels and occurred in the following order: prose recall immediate, N-back (0-back, 1-back, 2-back), delay discounting, Go/No-Go, prose recall delayed. Smoking was not permitted until the end of the session. All participants provided written informed consent. Ethical approval was given by UCL Ethics Committee (See Appendix C). Participants were reimbursed £10/hour. The experiment was conducted in accordance with the Declaration of Helsinki and all data was processed and stored according to the Data Protection Act 1998.

7.2.6 Statistical analysis

Statistical analyses were performed in the Statistical Package for Social Scientists (SPSS 23; IBM, Chicago, IL). Visual inspection of diagnostic plots was used to check for normality. Where sphericity was violated the Greenhouse Geiser correction was

used and degrees of freedom were rounded to the nearest integer. Outliers > 1.5 x interquartile range (IQR) were winsorized to the next highest value. Logged-k values (delay discounting) were used as the data showed a non-normal distribution. K was derived by plotting the subjective value against reward delays and using least squares non-linear regression to fit a curve to the data points; further information can be found in Reed et al. (2012). I conducted paired sample t-tests between both drug conditions and satiety, to confirm that abstinence increased withdrawal (see chapter 6). The prose recall, N-back, Delay Discounting and Go/No-Go were analysed using repeated measures ANOVA with a factor of drug (CBD, PBO) and additional task specific factors for the prose recall (immediate, delayed) and for the N-back (0 back, 1 back, 2 back). Interactions were explored via pairwise post-hoc comparisons, Bonferroni-corrected locally within each omnibus term to avoid an inflated Type I error rate. Order effects were analysed with drug order (CBD first, PBO first) as a between subjects factor. Exploratory analyses investigating the effects of past cannabis use were analysed with cannabis user (used cannabis in the past year, not used cannabis in the past year) as a between subjects factor. As I did not have any specific *a priori* hypotheses regarding covariates, I did not include any as per Kraemer (2015).

Scaled Jeffreys-Zellner-Siow (JZS) Bayes Factor was calculated for the main effect of drug (CBD vs. PBO) when it was not significant according to frequentist statistics (Buckingham et al. 2016; Lawn et al. 2017). This was calculated for the main variable of interest in each task (k, prose recall total, N-back total correct responses). I used a scaled-information prior of r = 1, recommended by Rouder et al. (2009).

7.3 Results

7.3.1 Demographics and Manipulation Checks

See section 6.3.1, Table 6.2 and Table 6.3.

Trait impulsivity as assessed by the Barratt Impulsiveness Scale (BIS-11) score was 75.17 (± 5.31). Trait anxiety as measured by the State Trait Anxiety Inventory-Trait

(STAI) was 40.93 (9.40). Carbon monoxide (CO) upon arrival was 4.27ppm (±2.23) for CBD and 4.17 (±2.69) for PBO (t(29)= .324, *p*= .748). Withdrawal, as measured by the Mood and Physical Symptoms Scale (MPSS) upon arrival was significantly greater under both CBD (12.03 ± 3.13) and PBO (12.13 ± 3.72) in comparison to satiation (9.97 ±2.86; both *p's*<0.05).

7.3.2 Delay discounting

There was no main effect of drug on k ($F_{(1,29)}$=0.065, *p*=.801, ηp^2=.002) suggesting no difference between CBD (M: 0.006, SE:0.001) and PBO (M: 0.006, SE:0.001). This was confirmed by Bayesian analysis which showed that the null hypothesis was 4.61 times more likely than the alternative given the data (JZS Bayes Factor: 4.61).

7.3.3 Go/no-go

There was a main effect of drug ($F_{(1,29)}$=4.721, *p*=.038, ηp^2=.140) which showed there were more commission errors after CBD (M: 2.600, SE:0.400) compared to PBO (M: 1.900, SE: 0.350).

7.3.4 Prose recall

There was no main effect of drug ($F_{(1,29)}$=1.410, *p*=.244, ηp^2=.046) suggesting no effect of CBD (M: 8.790, SE: 0.690) in comparison to PBO (M: 9.740, SE: 0.590). This was confirmed by a Bayesian analysis that indicated the null was 3.61 times more likely than the alternative given the data, providing evidence that CBD did not affect verbal memory (JZS Bayes Factor = 3.61). However, there was main effect of delay ($F_{(1,29)}$=57.020, *p*<.001, ηp^2=.660) which showed delayed recall (M: 8.283, SE:0.574) was poorer than immediate recall (M: 9.272, SE:0.574). There was no interaction between condition and delay ($F_{(2,58)}$=0.530, *p*=.471, ηp^2=.018).

7.3.4.1 Order effects

Order effects emerged for the prose recall task. A drug x order interaction emerged when order was included as a between subjects factor ($F_{(1,28)}$=33.037, p<.001,

ηp^2=.540) which showed that the prose recall score was dependent upon which drug was received in the first session. To follow this up a session (one, two) x drug order (CBD first, PBO first) mixed ANOVA was conducted which showed a session x order interaction ($F_{(1,28)}$=5.032, p=.033, ηp^2=.015). This revealed a trend towards a difference between orders for session two (p=.098) wherein the participants who received CBD first improved to a greater extent on the second session than those who received placebo first (Fig 7.1). For session one, they were equivalent (p=.978). Additionally, practise effects for observed for both orders but those who received CBD first increased by 4.12 (SE: 0.75) idea units between session one and two (p< 0.001), and those who received PBO first increased by 1.75 (SE: 0.75) idea units between session one and session two (p=.026). No order effects emerged for the remainder of the tasks.

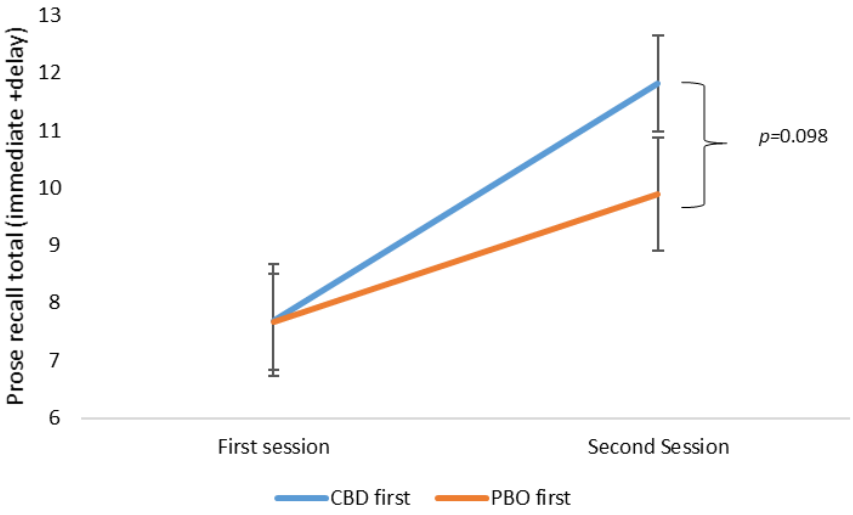


Figure 7.1. Order effects for the prose recall task. Error bars represent ± SEM.

7.3.5 N back

7.3.5.1 Correct responses

There was no main effect of drug ($F_{(1, 29)}$=0.532, p=.472, ηp^2=.018) suggesting no effect of CBD (M: 42.87, SE: 0.61) in comparison to PBO (M: 43.21, SE: 0.58). The lack of main effect of drug was confirmed by a Bayesian analysis which showed that null was 5.48 times more likely than the alternative hypothesis given the data (JZS Bayes Factor

= 5.48). There was a main effect of load ($F_{(1, 32)}$=53.022, p<.001 ηp^2=.646) which showed that correct responses decreased as a function of load (0-back M: 47.63 SE: 0.19, 1-back M: 43.32 SE: 0.48, 2-back M: 38.17 SE:1.27). There was no drug x load interaction ($F_{(2,58)}$=1.776, p=.178, ηp^2=.058).

7.3.5.2 Reaction time

There was no main effect of drug suggesting no difference between CBD (M: 527.93, SE: 18.85) and PBO (M: 531.84, SE: 14.52). This was confirmed by a Bayesian analysis which showed that the null was 6.66 more likely than the alternative (JZS Bayes Factor: 6.66) There was a main effect of load ($F_{(1, 41)}$=96.811, p< .001, ηp^2=.769) which showed that RT increased with load (0-back M: 412.57 SE: 12.63, 1-back M: 536.61 SE:16.86, 2-back M: 640.47 SE:24.11). No interactions emerged.

7.3.5.3 Maintenance and Manipulation

There was no main effect of drug for maintenance ($F_{(1,29)}$=0.118, p=.734, ηp^2=.004), suggesting no difference between CBD (M: -3.73, SE: 0.56) and PBO (M: -4.03, SE: 0.67). There was no main effect of drug for manipulation ($F_{(1,29)}$=3.047, p=.091, ηp^2=.095) again suggesting no difference between CBD (M: -6.73, SE: 1.39) and PBO (M: -4.40, SE: 1.36).

7.3.6 Exploratory effects of cannabis use

Given that more than half the participants (n=17) has a history of cannabis use, I additionally investigated individual differences based cannabis use history. History of cannabis use (no, yes) was included as a between subjects factor in the prose recall task and a drug x cannabis user interaction emerged ($F_{(1,28)}$=6.400, p=.017, ηp^2=.186). No other main effects or interactions emerged apart from the main effect of delay (see section 7.3.4). Exploration of the drug x cannabis user interaction using Bonferroni corrected paired t-tests showed that those with a history of cannabis use scored lower on prose recall when on CBD in comparison to PBO (Mean difference: 2.57, SE:

0.975;*p*=0.013) as can be seen in Fig 7.2a. Furthermore, a trend towards cannabis users performing better on placebo than non-cannabis users was also observed (mean difference:2.632, SE: 1.346;*p*=0.061) (Fig 7.2a)

In regards to the N back – a similar trend towards a drug x cannabis user interaction emerged ($F_{(1,28)}$=3.631, p=.067, ηp^2=.115). No other main effects of interactions emerged apart from for a main effect of load, similar to above (see section 7.3.5). Exploration of the drug x cannabis user interaction using Bonferroni corrected paired t-tests showed that those with a history of cannabis use scored lower when on CBD in comparison to placebo (Mean difference: 1.098, SE: 0.601;*p*=0.078) which can be seen in Fig 7.2b.

No effects of cannabis use emerged for the impulsivity tasks.

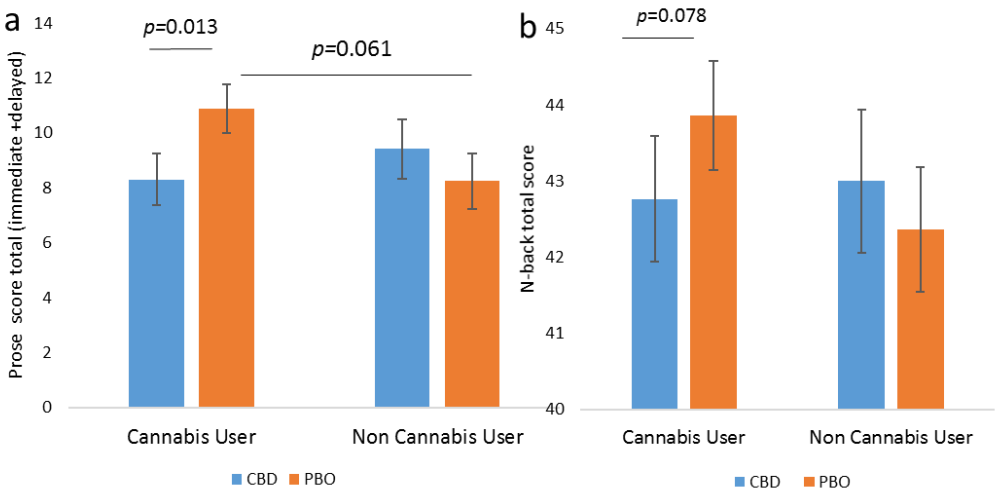


Figure 7.2. Exploratory analysis of the effects of CBD versus placebo in cannabis users (n=17) versus non cannabis users (n=13) on the prose recall task (a) and the n-back task (b). Error bars represent ± SEM.

7.4 Discussion

This study aimed to investigate if CBD, in comparison to placebo, would improve memory and reduce impulsivity in dependent cigarette smokers during tobacco abstinence. I selected tasks and domains that have been shown to be impaired during cigarette abstinence in a recent meta-analysis (Grabski et al. 2016). There were no effects of CBD on prose recall, spatial working memory (correct responses, reaction

time, maintenance and manipulation), or delay discounting tasks. I obtained evidence in support of the null for these comparisons using Bayesian analyses. Contrary to our predictions, however, CBD increased commission errors compared to placebo on the go/no-go task. Additionally, I observed order effects on the prose recall task which suggest that those who were randomised to be given CBD first, showed slightly greater improvement between session one and two, than those given placebo first, tentatively supporting the pro-cognitive effects of CBD. Finally, post-hoc and exploratory analyses revealed trends towards differential effects of CBD in comparison to placebo on both the prose recall task and the N-back task suggesting that cannabis users may not benefit from CBD as much as non-cannabis users.

Impaired response inhibition is an important etiological factor in tobacco dependence (Billieux et al. 2010; Powell et al. 2002; Powell et al. 2010). Response inhibition may be a key cognitive process during tobacco withdrawal as it requires inhibiting a pre-potent response e.g. automatically picking up a cigarette and/or inhibiting the urge to smoke. Response inhibition has been to shown to increase as a result of cigarette abstinence (Ashare et al. 2014). However, there were no beneficial effects of CBD on the number of commission errors. Indeed, I show here that CBD actually increased commission errors indicating greater impulsive action. This is an unexpected finding, that was quantitatively small, from a single study and therefore should be should be interpreted as preliminary evidence until it is replicated. Additionally, the task is designed such that only few commission errors can be made, giving little room for error. Furthermore, this study did not find that CBD modified responses on delay discounting – a measure of impulsive decision making.

Grabski et al. (2016) also showed impaired arithmetic and recognition memory ability, in abstinent smokers, interpreted by the authors as potential evidence for effects of abstinence on working memory. However, recognition memory also includes a component of verbal episodic memory. In the present study, there was no difference

between CBD and placebo on either verbal episodic and working memory. Previous research has suggested that CBD (in cannabis as well as synthetic) may protect against THC-induced impairments in verbal/recognition memory (Englund et al. 2013; Morgan et al. 2012; Morgan et al. 2010b). Order effects were observed between the two abstinent sessions for the prose recall task where if participants were given CBD in the first session, then they performed better in the second session. However, if participants was given placebo in the first session, then they will still improve as a function of practise effects, however, the improvement was not as great as with CBD. These effects were found despite attempts to minimise practise effects between the two abstinent sessions. The generally null results of CBD on cognition here may not be surprising as the mechanisms responsible for the effects of CBD on cognition are poorly understood. The effects of CBD are not consistent for even its most well studied constructs such as lessening of acute anxiety (Hundal et al. 2017). They likely are dependent on experimental setting, dose, dosing regimen, route of administration, the population studied; whether CBD is given in combination with THC and finally whether synthetic versus whole plant CBD is used. Given that the cannabis plant contains hundreds of compounds including terpenes and flavonoids, it may be that CBD derived from plants (such as the soon-to-be approved, Epidiolex), may be more effective than synthetic CBD.

Some participants had a history of cannabis use, although all participants passed a urine drug screen and no participants had used cannabis in the past month. Interestingly, post-hoc analyses showed that cannabis users benefited less from CBD than placebo on both the prose recall and N-back tasks or alternatively, acute CBD may be detrimental to the memory of cannabis users. This contradicts previous research, which suggests that CBD when combined seems to protective against memory impairments in cannabis users (Englund et al. 2013; Morgan et al. 2012; Morgan et al. 2010b). Regular cannabis users do show impaired structural and functional connectivity between the hippocampus and other brain areas (Lorenzetti et al. 2016), however, the

cannabis users in this study were not regular or current cannabis users. It should be noted that this analysis was not hypothesis-driven and there were differing numbers of cannabis users and non-cannabis users in the sample. This finding needs to be replicated in hypothesis-driven research designed to investigate if individuals who use cannabis may not benefit as much as non-cannabis users on memory during nicotine withdrawal.

The strongest evidence for the utility of CBD within addiction may arise from those tasks specifically associated with the motivational salience of cues associated with drug use (Chapter 6) (Hurd et al. 2015; Morgan et al. 2010a; Ren et al. 2009). For example, Ren et al. (2009) conducted a preclinical study investigating heroin self-administration and found that although self-administration itself was unaffected by CBD, cue-induced heroin-seeking behaviour and reinstatement were both reduced. CBD also inhibited relapse behaviour during active heroin intake. In regards to human research, Hurd et al. (2015) conducted a pilot double-blind, placebo-controlled investigation in opioid-dependent individuals who were abstinent for 7 days. They found that cue-induced craving was significantly reduced after a single administration of CBD, and this persisted for 7 days. In regards to the effects of CBD on cigarette smoking, Morgan et al. (2013a) found a 40% reduction in cigarettes smoked after one week of ad-lib CBD inhaler vs. placebo, however no mechanisms were investigated. The study was based on previous research showing that higher levels of CBD in smoked cannabis reduced the wanting and liking of cannabis related stimuli (Morgan et al. 2010a). Finally in chapter 6, I found that CBD reversed attentional bias away from cigarette cues, compared to placebo, in abstinent dependent cigarette smokers. Participant's attentional bias under CBD was therefore no longer different from satiety. Moreover, I found a reduction in explicit "liking" of cigarette cues. Taken together, these findings are consistent with the possibility that CBD has utility in modifying the salience of drug cues and not necessarily with the modulation impulsivity. One of the reasons this seems plausible is because this may also be the mechanism by which CBD affects symptoms

in psychosis which has also been seen as a disorder of aberrant salience (Kapur 2003). Further investigation is required to confirm this.

7.4.1 Strengths and limitations

This study has several methodological strengths including using tasks and domains that have been previously been shown to be impaired during tobacco abstinence (Grabski et al. 2016). Furthermore, this study had a moderately large sample size in a crossover design, informed by a power calculation and inflated by 50% to account for “winner’s curse”. The experimental medicine design of the study allowed for an economical and mechanistic evaluation of CBD on tobacco withdrawal. Finally, abstinence was confirmed by biological verification (carbon monoxide). However, there are also some limitations. Given the incompletely elucidated mechanism of CBD, the present study may have not selected the correct dose for therapeutic effects. There has only been one published dose-response study of CBD in humans, which was specifically designed to test the anxiolytic effects in public speaking, and this only tested three doses (Zuardi et al. 2017). Therefore, dose selection generally copies that used in previous single-dose studies. The dose-response effects of CBD may follow an inverted U shaped curve, and thus our 800mg dose may be too high for the therapeutic dose window (Zuardi et al. 2017). Associated with this, only a single dose of oral CBD was investigated. I did not collect plasma to monitor the pharmacokinetics of CBD. However, this study was informed by previous pharmacokinetic data from the same 800mg oral dose of CBD (Babalonis et al. 2016). Furthermore, only a single dose of the drug was given, and it may be that CBD is more effective with repeated dosing (Zuardi et al. 2017). Future research should investigate multiple doses and repeated administration to reach plasma concentrations that are at a steady-state.

7.4.2 Conclusion

In conclusion, this study found that in dependent cigarette smokers who were abstinent overnight, CBD did not improve cognition on tasks that have been shown to be impaired

during cigarette abstinence confirmed by Bayesian analyses in support of the null hypothesis. This research suggests that CBD is not efficacious in reversing the cognitive impairments associated with acute nicotine abstinence in cigarette dependent individuals.

Chapter 8: General discussion

I set out to examine the interactions between cannabinoids and nicotine/tobacco utilising mixed methods (observational and experimental). I have added to the small body of research regarding the recreational combination of cannabis and tobacco as well as the effects of modulation of the eCB system for nicotine withdrawal with CBD. In this discussion, I will firstly summarise the findings based on each of the six research questions outlined in the introduction. Secondly, I will integrate the results into the literature focussing on memory, psychosis and addiction. I will then discuss conceptual and measurement issues that were raised whilst conducting this research. Finally, I will give an overview of the strengths and limitations of the studies, future work and clinical implications.

Although cannabis and tobacco are two of the world's most popularly used drugs, the known data regarding their combined use has been elusive. This thesis provides the first investigation of this relationship in human psychopharmacological research with a controlled dose of the drugs using and an ecological method of administration. Furthermore, CBD, the non-intoxicating, antipsychotic and anxiolytic cannabinoid in cannabis, has recently been under huge investigation as a novel antipsychotic and drug addiction treatment, however, important human translational steps of understanding the drugs mechanism, had been missing.

8.1 Summary of findings

How do routes of administration of cannabis and tobacco vary across the world and does this influence motivation to quit the use of either drug?

In chapter 2, I used data from the Global Drug Survey 2013 to investigate how recreational cannabis smokers used cannabis, with and without tobacco, and via what ROA. I found marked variation in how people used cannabis around the western world. There are several take-home messages from this study; across all countries with greater than 500 respondents, tobacco ROAs were more popular that non-tobacco

ROAs (65.6 vs 32.1%). Tobacco ROAs were predominant in Europe (80.9% in Switzerland to 77.2% in the UK) and the most popular ROA was smoking joints with tobacco (61.3%). Non-tobacco routes were more popular in the Americas (78.2-92.1%). I further investigated how ROA was associated with motivation to quit cannabis or tobacco, whilst controlling for a variety of confounders including age, sex, days of cannabis, tobacco, and tobacco with cannabis use. In this analysis, I found that using a cannabis combined with tobacco was associated with reduced motivation to quit smoking *tobacco* and overall more negative effects of cannabis. Interestingly, tobacco ROAs were not consistently associated with a higher motivation to quit cannabis. Therefore, I was further motivated to investigate the effects of cannabis and tobacco using experimental research methods.

What are the individual and combined effects of cannabis and tobacco on memory and psychotic-like experiences?

In chapter 3, I reported results from a double-blind, placebo-controlled, four-way crossover study of the individual and combined effects of cannabis and tobacco on episodic and working memory and psychotomimetic symptoms. I was able to replicate a well-known finding that cannabis impairs verbal memory. Using a hypothesised *a priori* contrast, I showed that tobacco offset the effects of cannabis on delayed recall, suggesting that tobacco was only affecting retrieval of information that had previously been successfully encoded. In regards to working memory, I found that cannabis load-dependently reduced working memory, and tobacco improved working memory across all loads. However, tobacco did not offset the negative effects on working memory. Tobacco also did not offset or increase effects on cannabis–induced psychotic like symptoms. Cannabis and tobacco had independent effects on increasing heart rate and interacting effects on diastolic blood pressure; suggesting that using the drugs together led to poorer cardiovascular health. Importantly, tobacco did not influence subjective

pleasurable ratings of cannabis. These results suggest that tobacco may compensate for the negative cognitive effects of cannabis, but increases cardiovascular harms.

What are the individual and combined effects of cannabis and tobacco on reward processing and craving?

In chapter 4, I aimed to investigate how both drugs, affected ones 'wanting' (as indexed by purchase tasks) and 'liking' (as indexed by pleasantness rating task) of both drug and non-drug rewards – in particular, food. Relative to placebo cannabis, active cannabis reduced liking of cannabis stimuli, and increased response time to cannabis, food and neutral stimuli but, surprisingly, not to cigarette stimuli. Active cannabis also decreased demand for cannabis (i.e. how much cannabis one would consume for no cost and one's sensitivity to changes in price) and reduced demand for cigarettes (maximum expenditure and how many cigarettes one would consume if they were free). However, tobacco had no effect, either alone or combined, on drug liking or demand. Overall, this suggests that participants under the influence of cannabis, participants became more sensitive to price increases and therefore less likely to buy cigarettes or cannabis at higher prices. The results challenge a long-held belief that adding tobacco to cannabis increases its rewarding effects, which was confirmed by null effects of tobacco on ratings of "euphoric" and "stimulated". Given that participants were non-dependent cannabis and tobacco co-users, these results may suggest some cross-satiety.

How do recreational cannabis and tobacco co-users estimate dose of cannabis and tobacco in joints?

In chapter 5, it became clear to me that major gaps exist in the measurement of cannabis exposure especially in the lack of attention given to quantity measures in comparison to frequency measures. In this study, I further developed the "substitute method" to account for both cannabis and tobacco, specifically in "joints". I found that individuals overestimate the amount of cannabis that they put in a joint i.e. they were

reporting double the amount if cannabis that they rolled in a joint. However, they were accurate in recording the amount of tobacco that they rolled in a joint. This over-estimation was maintained across all drug conditions. Compared with placebo cannabis, active cannabis reduced both the actual dose of cannabis and of tobacco. Participants accurately estimated the reduction for tobacco, not for cannabis. Active tobacco had no effect on cannabis or tobacco in joints. The “roll a joint” paradigm is a novel, simple and actionable paradigm I developed that should now be used to assess dose per joint. The paradigm is now being used in several studies in the UK, US, Australia, which will further validate its use.

What are the effects of CBD on tobacco withdrawal, craving and attentional bias after overnight abstinence?

In chapters 6 and 7, I wanted to focus on treatment mechanisms by investigating how CBD, the major non-intoxicating cannabinoid, could be used in a therapeutic manner to treat tobacco use disorders. Withdrawal from nicotine, even within a few hours, leads to cognitive and affective symptoms. CBD has properties that may make it an ideal drug for withdrawal such as its anxiolytic effects. Using an experimental medicine study design, I hypothesised that CBD would reduce withdrawal symptomology, including attentional bias and craving, in comparison to placebo, in nicotine dependent participants who had been abstinent overnight.

In regards to attentional bias, I found that abstinence increased bias towards cigarette stimuli, as expected. CBD reversed this effect, such that automatic attentional bias was directed away from cigarette cues and no longer differed from satiety. Compared with placebo, CBD also reduced explicit pleasantness ratings of cigarette images, a measure of drug “liking”. Craving and withdrawal were unaffected by CBD, but greater in abstinence compared with satiety. Systolic blood pressure decreased under CBD during abstinence. These results give impetus for further research on the use of CBD in smoking cessation.

What are the effects of CBD in comparison to placebo on attenuation of the cognitive effects of nicotine abstinence?

In chapter 7, I investigated cognitive indicators of nicotine withdrawal that had been validated by meta-analysis, particularly memory and impulsivity. Both may be important triggers of relapse during smoking cessation attempts. Participants, after overnight nicotine abstinence, were assessed on verbal episodic (prose recall), working memory (n-back) and impulsivity (delayed discounting and the go/no-go task); measures of impulsivity. There were no effects of CBD on prose recall, spatial working memory or delay discounting, and this was confirmed by Bayesian analysis in support of the null. Contrary to our hypothesis, CBD increased commission errors compared to placebo on the go/no-go task suggestive of greater motor impulsivity. Finally, order effects on the prose recall task were observed which showed that those who received CBD first showed slightly greater improvement between session one and two, than those given placebo first, tentatively supporting the pro-cognitive effects of CBD.

Together chapters 6 and 7 give an insight to the possible treatment target of CBD in the treatment of addictive disorders. The strongest evidence for CBD's therapeutic was found on motivational salience of cues associated with drug use. CBD was relatively less useful for withdrawal-induced cognitive impairments.

In summary, in this thesis, I provide evidence for the observational and pharmacological interactions between cannabinoids (both THC and CBD), tobacco and nicotine withdrawal. In the following section, I have integrated these novel findings with the existing literature available prior to my thesis, as previously introduced in chapter 1.

8.1.1 Cannabis, tobacco and memory

I replicated previous studies showing the impairments produced by cannabis in verbal episodic and working memory (Broyd et al. 2016; Curran et al. 2002a; D'Souza et al. 2004; D'Souza et al. 2008; Hart et al. 2001). I also replicated enhancements induced by nicotine (Heishman et al. 2010). Specifically I found evidence to support my

hypothesis that nicotine would offset the effects of cannabis on verbal recall. However, this finding emerged for delayed but not immediate recall. This suggested that nicotine is affecting retrieval of previously correctly encoded material and not the encoding of new information. Additionally, I found opposite independent effects of cannabis and tobacco on working memory, which did not interact with each other. Indeed the tobacco effects seem to be a result of increased attention because of the equivalent size of the effect across all loads on the n-back. Cannabis can affect both immediate and delayed recall, but immediate recall remained intact in these studies therefore it may also be that the measures used were not sensitive enough to pick up effects on encoding. Previous research using list-learning have shown THC effects encoding (Ranganathan et al. 2017). Additionally, delayed recall is a more cognitively demanding task than immediate recall; therefore we may only see effects of nicotine/THC when higher cognitive load is required. Delayed recall also involves other processes including working memory and attention.

My findings suggest there is minor facilitation via tobacco on the acute effects of cannabis on memory. It is important that future research investigate other types of memory. As to whether these memory changes perpetuate co-use is a matter for longitudinal research. I would propose an investigation of co-use and cognition over time. Given that in chapter 4, we found that in this population of non-dependent users, the acute effects of tobacco had minimal effects on cannabis-associated reward and motivation to use the drug; it seems that this relationship is not driven by drug-related motivation and reward. This pattern could change with dependency on cannabis, tobacco, or both. Additionally, in chapter 2, I observed that tobacco-based ROAs (i.e. a combination of cannabis + tobacco) were not associated with motivation to quit cannabis, but were associated with motivation to quit tobacco. This research also implies that investigations of cannabis on cognition should be reporting and statistically controlling for tobacco use as a factor. One interesting question to ask is: who are the individuals who get more enhancing effects of tobacco on cannabis? Are those the

individuals who become dependent on both drugs because of these beneficial cognitive effects? In regards to future research, the first step would be to replicate this study in dependent cannabis and tobacco users. Another angle may be to investigate the effects nicotine on pre-loaded cannabis, as individuals report smoking cigarettes to maintain a cannabis high, sometimes referred to as ‘chasing’.

I used the known effect of nicotine withdrawal on memory (Grabski et al. 2016) and the fact that the endocannabinoid system is highly involved in learning and memory (Mechoulam and Parker 2013) to investigate if CBD could improve the memory-based symptoms of nicotine withdrawal (chapter 6). On verbal episodic memory, I found tentative order effects, which point towards a protective role of CBD in verbal episodic memory. However, this was a post-hoc analysis that I did not powered the study to detect (and it was not significant, but a trend), and therefore should be treated with caution until replicated. Those who received CBD first, showed a larger improvement between the sessions then those who received placebo first. This supports research suggesting that CBD has pro-memory effects. For example, individuals with CBD in their cannabis show lower memory impairment than those who do not using the same tasks (Morgan et al. 2010b), additionally preloading of CBD before THC protects against the negative effects of THC on memory (Englund et al. 2013). Furthermore, Das et al. (2013) found that CBD enhances consolidation of extinction learning, also evidence of a pro-cognitive effect.

I am not trying to suggest that the cognitive changes in nicotine withdrawal and the memory impairments induced by THC are the same but, episodic memory, as measured by the prose recall task, involves multiple processes including sematic integration, working memory and episodic memory, and both NAChRs and CB1R are densely populated in both the hippocampus and the cortex.

One unexpected post-hoc result from chapter 7 was that CBD administration led to poorer prose recall and N-back scores, in comparison to placebo, only in those with a

history of cannabis use, in comparison to those who had never used cannabis. Daily cannabis use leads to CB1 downregulation (~20% vs controls) in the hippocampus, where CB1 receptors are densely populated – consistent with the classical effect of cannabis on memory (Hirvonen et al. 2012). However, CB1 downregulation was reversed with four weeks of abstinence (Hirvonen et al. 2012) with some research suggesting that CB1 downregulation can be reversed within two days (D'Souza et al. 2016). The effects of cannabis on memory are also reverse with 4 weeks of abstinence (Schreiner and Dunn 2012). Given that my participants had not used cannabis in the last 100 days and passed a urine drug screen, this specific result may have been a spurious finding which I was not powered to investigate, a result of acute administration of CBD, or some other underlying factor that manifested itself as an effect of history of cannabis use. Although, this may have been a spurious/under-powered finding, it also generates a novel hypothesis that there may be differential effects of CBD in those with a history of cannabis use. This is important, as it may inform us about for whom CBD has the most applicability.

8.1.2 Cannabis, Tobacco and Psychosis

The relationship of cannabis and tobacco to schizophrenia and first episode psychosis is a field that is currently significant interest and debate. At the population level, there are independent associations between cannabis use and schizophrenia where those who smoke cannabis regularly have a 2- to 3-fold increased risk of a psychotic outcome (Moore et al. 2007). Furthermore, recent evidence that there is a similar relationship between tobacco and schizophrenia, which suggest that tobacco use, rather than a consequence of psychosis (as reviewed in chapter 1), may also be a cause of schizophrenia. I found that cannabis increased psychotic-like symptoms, as expected, and this was not modulated by tobacco. This is similar to research showing acute nicotine did not have an effect on ketamine induced psychotic-like symptoms (as both are theoretical models of psychosis and both drugs mimic effects of psychosis)

(D'Souza et al. 2012a). Furthermore, it supports research showing that acute nicotine administration via cigarette smoking and nicotine sprays had no effect on the overall symptomology in individuals with schizophrenia (Smith et al. 2002). However, the idea was biologically plausible, as both cannabis and tobacco have been shown to increase dopamine (although sometimes inconsistently (Nutt et al. 2015)), leading to D2 super sensitivity and excessive dopamine is causal in psychosis (Novak et al. 2010).

Some might argue that because there is evidence on a population level, this does not necessarily mean it is evident at a biological or behavioural level. However, it is important to triangulate research such that the same hypothesis can be investigated at several levels of investigation– from populations level epidemiology to cellular biology (Munafò and Smith 2018). Alternatively, it may be that the original results, which suggest that tobacco is a causal factor in schizophrenia, are not as strong as suggested. Indeed, these results are often reduced when studies control sufficiently for confounding by other variables as well evidenced in Gage et al. (2014) and Hickling et al. (2018). In my opinion, there is still a lack of evidence here, because there has yet to be a study that fully separates cannabis from tobacco (in joints) in epidemiological research on psychosis. This is because the cohort studies are not assessing cannabis with enough detail. However, this was possible in my acute psychopharmacological interaction research. Finally, clinical schizophrenia and psychotic-like symptoms in healthy participants induced by cannabis (which were investigated in this thesis) are relatively far removed from each other.

Although not a primary focus of this thesis, in hindsight, I should have utilised my experimental designs to try to model their relationship to psychotic-like symptoms for example by investigating nicotine withdrawal symptomology in individuals with first episode psychosis.

8.1.3 Cannabis, Tobacco and Addiction

Reward processing, motivation and addiction have been of core importance throughout this thesis. In Robinson and Berridge's framework, incentive salience processes and the explicit desire for drugs (craving, attentional bias and potentially purchasing behaviours) and "liking" are dissociated. In this thesis, I have aimed to capture both of these processes in the acute studies to try and investigate a) whether cannabis and tobacco together are more rewarding then individually – and how this is related to hedonistic processes and b) whether CBD modulates cigarette salience and explicit liking.

Cannabis and tobacco together were not more rewarding than cannabis alone as indexed by acute subjective effects of "stoned" or "euphoric" or stimulated". This is important because there is a myth that adding tobacco to cannabis will make one more stoned. For example, a simple google search for "cannabis and tobacco" provides links to websites such as herb.co (https://herb.co/marijuana/news/smoke-weed-and-tobacco), which raises the question, "Do spliffs give a different high?" to its readers. I found that it does not improve the subjective experience of cannabis, despite the information on the internet. Using the principals of behavioural economics, we administered purchasing tasks and delayed discounting tasks throughout to assess drug "wanting". In hindsight, these tasks were very sensitive to satiety leading to a huge proportion of missing data when individuals said they would not buy any cannabis or tobacco, and therefore were not useful in the acute drug administration studies among non-dependent users. Furthermore, there were trend level associations between the behavioural economic measures and my acute drug manipulations potentially suggesting weak or spurious effects. These studies were originally powered by a previous four way cross over (investigating if CBD protects against THC on emotional processing; Hindocha et al. (2015a)) and were not powered to detect smaller effects

such as those on purchasing tasks. The alternative hypothesis may also be true which is that the drugs together do not effect drug wanting, more than each drug alone.

I also assessed the explicit liking of reward through Pleasantness Rating Tasks. The hedonistic aspects of drugs (i.e. liking) have been far less investigated than the "wanting" aspect, so there was little to compare my research with. Therefore, these results were difficult to interpret apart from in regards to satiety. One interesting result that I found was an increase in response time to all stimuli (cannabis, neutral and food) apart from cigarette-related stimuli after active cannabis had been consumed. Cannabis increased response time due to the acute effects of THC on motor response – a simple behavioural effect that was expected from the drug. However, this did not occur for cigarette stimuli, suggesting an automatic bias away from cigarette stimuli or perhaps a self-identity issue within the selected participant group of non-dependent cannabis and tobacco users.

Young cannabis users who put tobacco in their joints do not consider themselves tobacco smokers or indeed co-users (Akre et al. 2015; Akre et al. 2010). They express that the reason they use cannabis with tobacco is to facilitate burning or because it is how they learnt to smoke. This is evident in a qualitative study of why people smoke cannabis and tobacco - "*You learned to roll a joint with tobacco, so you put in tobacco like everybody else* (male, 19 years old)" (Akre et al. 2015) and also in quantitative examinations of co-use (see table 8.1).

Table 8.1: Data from the Nicotine and Marijuana Interaction Expectancy (NAMIE) scale (Ramo et al. 2013) administered in association with chapter 3-5 (n=24 non-dependent co-users). Participants ranked the three most important reasons for using cannabis and tobacco together in joints. Data is ordered by weighted importance from most important to least important (% of participants).

	Most Important	**2nd Most Important**	**3rd Most important**
1 It improves the 'smokeablity' of my cannabis	29.2	16.7	16.7
2 It makes by cannabis go further	29.2	16.7	8.30
3 It's the way all my friends smoke	12.5	29.2	16.7
4 It's the way I started using	12.5	20.8	20.8
5 It's convenient	12.5	12.5	16.7
6 It's the only way I get to smoke tobacco	4.20	0.00	4.20
7 I smoke cigarettes as well so I think it reduces my tobacco smoking	0.00	4.2	4.20
8 I prefer the effect to cannabis on its own	0.00	0.00	12.5

The data in table 8.1 was collected during my PhD and shows the reasons why people might consume cannabis and tobacco together. The hedonistic aspect of "pleasantness" is captured in the last option i.e. cannabis and tobacco together are more pleasurable that cannabis alone, however almost no-one ranked this as an option, instead most ranked pragmatic convenience options. This suggests that recreational cannabis and tobacco co-users may not be mixing because they "like" that combination. Thus, challenging the myth that both drugs together are more pleasurable (see option 8, table 8.1).

Another reason why these studies may not have found effects of tobacco on reward processing is due to the tightly controlled experimental design in where I specifically manipulated nicotine, not tobacco. Thus, cannabis users had no subjective insight into whether nicotine was present or absent. Participants always smoked tobacco in every experimental session, but half the time it was denicotinized. If I had modified tobacco, for example, by using an inactive non-tobacco based filler, I may have seen differential

effects on reward processing. However, this would have made the blinding redundant and I wanted to conduct a carefully controlled experiment. Tobacco has many more harmful chemicals in it which contribute to the smoking experience and although nicotine is the primary addictive component of tobacco, it may not be sufficient to maintain the psychophysiological need to smoke (Domino et al. 2013). An alternative method of examining this relationship would be to remove the aspect of smoking altogether and use IV THC and nicotine, similar to D'Souza et al. (2012a).

The amount of tobacco used by co-users in these studies is notable. In chapter 5, I estimated that participants (recreational co-users) were adding, on average, 0.35g tobacco per joint, equivalent to roughly one third of a cigarette. Participants also self-reported smoking joints, on average, 7 times per month leading to an estimated 3 cigarettes as a result of smoking joints. Additionally, these participants reported about smoking, on average, about 2 cigarettes per day on 11 days per month, leading to an estimated 25 cigarettes per month. This exposes participants to cotinine (a nicotine metabolite) levels that are suggestive of moderate tobacco exposure - equivalent to that found in light or moderate cigarette smokers (Bélanger et al. 2011). This is an important observation because the development of symptoms of nicotine dependence are also observed in chippers (Shiffman 1989).

If I were to conduct this research again, instead of administering cannabis and tobacco both individually and combined to recreational users – which robustly led to satiety, and therefore a reduction in “wanting” and “liking”. I could have asked dependent cannabis and tobacco co-users to abstain from tobacco, and tobacco users to abstain from cannabis and then assessed cue-induced craving and self-administration which would have provided a direct demonstration of the abuse potential of the drugs combined relative to their components.

8.1.4 CBD at the intersection of psychosis and addiction

As previously discussed, the attribution of salience towards drug-related stimuli has been assessed in several ways in this thesis. Some have hypothesised that salience attribution is underpinned by dopamine release, which leads to craving and drug use (Robinson and Berridge 2001). At the same time, one of the major theories of human schizophrenia suggested by Kapur (2003), is the idea of aberrant salience. This theory suggests that excessive dopamine signalling the striatum leads to excessive motivational salience assigned to innocuous stimuli – giving them salience/importance. Interestingly, this may be the common biological substrate that underlies both tobacco smoking and psychosis (Freeman et al. 2014a; Kapur 2003) which is said to contribute to positive psychotic symptoms. This may be a candidate mechanism for treatment by CBD. Previous research suggests that CBD modulates activity in the areas of the brain associated with salience attribution during an attentional salience task (Bhattacharyya et al. 2012; Bhattacharyya et al. 2015; Morgan et al. 2010a).

Preliminary research suggest that CBD has been shown to be as effective as a leading antipsychotic; amisulpride (Leweke et al. 2012) for treating psychosis. When combined with antipsychotic treatment, it can improve outcomes in patients with psychosis in regards to their positive symptoms, clinician's ratings and overall cognitive performance (McGuire et al. 2018), however negative trials have also been reported (Boggs et al. 2018). At the same time, I have shown that CBD may modulate the salience of smoking cues (chapter 6). Therefore, CBD may have particular promise in helping people with a diagnosis of psychosis to stop cigarette smoking. In order to investigate this experimentally, one would require a task that that indexes aberrant salience (Roiser et al. 2009). This would allow investigation of the salience and attentional processes underlying drug addiction and psychoses which may both be treated with CBD (Freeman et al. 2012a). Currently unpublished results from a clinical trial investigating CBD as a treatment for cannabis dependence in young people, which I contributed to

prior to my PhD, shows that CBD (in comparison to placebo; and in combination with motivational interviewing), is effective at increasing the number of days abstinent in cannabis users. This may also be due to a reduction in salience of cannabis cues and requires further investigation.

Therefore, converging lines of evidence suggests the next appropriate step in CBD research is in clinical trials of CBD for tobacco use and/or cannabis use in schizophrenia. Smoking cessation amongst people with severe mental health problems has proved challenging as evidenced by the high number of cigarette smokers in people with severe mental health problems (Brose et al. 2018; Faith Dickerson et al. 2018). Indeed, 70% of those with severe mental health problems discharged from hospital after a period of abstinence relapsed on the day of discharge (Brose et al. 2018). If the withdrawal period can be improved, alongside symptoms of severe mental health/psychosis, then CBD could become the first drug treatment for dual-disorders. This would be very similar to current smoking cessation treatments, which target withdrawal. The proposed mechanism, suggested throughout my thesis, is that CBD increases FAAH inhibition and therefore inhibits anandamide uptake leading to increased extracellular anandamide availability. This mechanism has been proposed for CBDs antipsychotic effects, this may (or may not) be the same as the mechanism in addiction and needs to be further investigated. This is particularly important because CBD has a wide pharmacological profile with many targets.

There are other FAAH inhibitors that have shown to attenuate symptoms of cannabis and opioid withdrawal in animals (Ramesh et al. 2013; Schlosburg et al. 2009). Although initial trials showed, the safety and tolerability of FAAH inhibitors in humans, and that it could be blocked by a PET radio ligand (Boileau et al. 2015; Huggins et al. 2012; Li et al. 2012). Most research regarding FAAH inhibitors was halted after a phase I study left one healthy volunteer dead and several others with irreversible neurological damage in January 2016 (Moore 2016). Just like with rimonabant, it seems drugs that designed to

modulate the endocannabinoid system can have unpredictable or serious adverse outcomes and this is may be because of the wide-ranging modulatory role of the endocannabinoid system. However, CBD has an excellent safety profile as supported by chapter 6 in this thesis – therefore providing an alternative to synthetic FAAH inhibitors.

As I suggested in the discussion sections of chapter 6 and 7 and the general introduction; the effects of CBD on the outcomes that we measure are not always consistent. This has also been noted by Hundal et al. (2017). They randomised participants, selected for high paranoid traits, –to receive CBD (600mg) or placebo. Participants took part in a virtual reality to assay persecutory ideation and anxiety. CBD had no impact apart from a trend towards increased anxiety. Indeed, in chapters 6 and 7, we found no effect of CBD on withdrawal-induced anxiety, and CBD increased errors on the Go/no-go task, a measure of motor impulsivity. This lack of consistency could be due to a wide variety of reasons, some of which include:

a) dosing and dosing schedule – single dose administration may not allow for steady state of CBD in plasma and multiple dosing may be required
b) low bioavailability in the oral form – vaping CBD may have higher bioavailability, however it produces a cough (Solowij et al. 2014)
c) Timing of drug administration relative to timing of tasks – time to peak CBD is around 150 minutes, but this could vary on individual differences such as FAAH polymorphism.
d) Inverted U-shape dose response curve of CBD - which means that at low and high doses, CBD may have an effect that is different to a moderate dose. However, how the doses in these three categories are still unclear (Zuardi et al. 2017)

e) Endocannabinoids are generated on demand, unlike other neurotransmitters, and therefore, the effects of CBD, may only be evidence when they are "needed", for example to buffer against stress and anxiety (Hillard 2018)

f) The entourage effect – different results may be seen with whole-plant derived CBD and synthetic CBD because whole-plant CBD includes terpenes and flavonoids. This may bolster the effect and therefore reduce the dose required.

In summary, although there are hopes that the research on CBD in mental health will be translated into the clinic, there is still further research that needs to conducted across the translational pipeline, before its use in the clinic is feasible. One of the most necessary steps would be a synthesis and critical review of the literature that clearly distinguishes between oral synthetic CBD, plant-derived CBD, CBD within cannabis and THC/CBD concentrations.

8.2 Conceptual issues

8.2.1 What is a co-user?

> *"Dependency is different between cannabis and tobacco, but one has to say that we always smoke joints with tobacco, so the boundary is pretty ambiguous" (male, age 21). Akre et al. (2010)*

Terminology in this area of research can be confusing. In designing these studies, it became evident that there was no clear definition on what it is to be a co-user. In the introduction, I used the following definitions:

Co-use: an umbrella term to refer to the use of both cannabis and tobacco.

Concurrent use is defined has the use of both substances individually e.g. smoking cannabis and smoking cigarettes.

Combined use to describe the use of cannabis and tobacco in a single product, such as a joint or spliff (cannabis and tobacco mixed together in rolling paper and smoked

i.e. to be co administered within the same product) or as a blunt (hollowed out cigar filled with cannabis).

However, there are problems with these definitions as many individuals are both concurrent and combined users. This potentially represents a new level of risk that is not represented in the binary divide above. Take, for example, two individuals, one who smokes cannabis in a bong and 2-5 tobacco cigarettes per day, and a second who smokes several joints per day and does not smoke cigarettes separately. Do these two individuals have the same level of exposure to tobacco? Additionally, is someone who uses a cannabis vaporizer and an e-cigarette, defined as a co-user of cannabis and nicotine? It would be naïve to consider these all individuals as having the same level of risk for addiction and cardiovascular issues associated with co-use. The reason for making these distinctions in types of cannabis-tobacco co-users is important because it effects prevalence rates in epidemiological studies. Combined use has only recently been investigated in the US, and are still an unknown in the UK, even with the data provided in chapter 2. Therefore, the representative survey studies regarding co-use in the US select those who smoke cannabis and cigarettes separately i.e. concurrent users (Agrawal et al. 2012; Peters et al. 2014; Schauer et al. 2016; Schauer and Peters 2018; Schauer et al. 2017; Singh et al. 2016). Indeed, some of these individuals could be smoking cannabis and tobacco in a combined manner too, but these people are a hidden population. I find this noteworthy because combined users may be at more harm than the concurrent users. Meier and Hatsukami (2017) suggest that co-use is actually a continuum, which varies in the heaviness of cannabis and tobacco use, route of administration and on the “toxicant exposure, drug use history, perception of harm and quit trajectories”. Thus, one study that I would propose involves a large online sample of co-users who vary in cannabis/THC and tobacco/nicotine exposure, then discovering the underlying latent classes and using the classes to predict long-term outcomes.

A potential implication of this field of research is on diagnostic criteria as defined by the current DSM. Given that the comorbidity between cannabis and tobacco is one of the most common, this may suggest that it is time to include Cannabis-Tobacco Use Disorder (CTUD) as its own entry into the DSM. Co-morbidity is one of the greatest criticisms of the DSM-5, and research is now moving away from these discrete categories, with the advancement of the Research Domain Criteria (RDOC) (Insel 2014). The National Institutes of Mental Health (NIMH) has proposed domains of functioning as a way to conceptualize the overlap between comorbid conditions and inform treatment selection. Indeed, there is a specific initiative for addiction called the Addiction Neuroscience Assessment (Kwako et al. 2016).

A second problem with the definitions is that it effects recruitment into studies. In chapters 6 and 7, I had originally intended to recruit tobacco users who did not smoke cannabis but I took advice from a co-author on the paper who had developed a human laboratory model of smoking cessation and who's meta-analysis I based the final two chapters are based on (Grabski et al. 2016). She found that 50% of dependent cigarette smokers who were telephoned-screened decided not to take part because they would not be able to abstain from cannabis use for two weeks. Although in chapter 6 and 7, we ensured participants have a negative urine screen and had not smoked cannabis in the past month, in would have been more difficult to recruit tobacco users who had never used cannabis. Indeed, having some participants who had used cannabis in the past led to an interesting post-hoc finding of cannabis users responding differentially to CBD and placebo.

Given the lack of consistency in this area regarding terminology, I would suggest that future research uses the Delphi Technique (Yücel et al. 2018) in experts to determine a consensus on the terminology in this area.

8.2.2 Novel ROAs

Usage patterns of tobacco, nicotine and cannabis products are constantly shifting against the back-drop of evolving product ranges, a fast growing cannabis industry and increasing legalization of cannabis. The research community has been slow to respond but needs to keep pace in order to develop harm reduction and treatment interventions (Walsh et al. 2017).

For example, since I published chapter 2 in 2016 and a corresponding letter entitled "Vaping cannabis (marijuana) has the potential to reduce tobacco smoking in cannabis users" (Hindocha et al. 2016b), the use of non-tobacco ROAs has continued to rise. However, the number of publications regarding co-use and cannabis vaping has barely increased such that I have still written 5% (37 total) of the papers that exist on PubMed about "cannabis vaping" as of 6th April 2018 (Fig. 8.1). The data for chapter 2 was collected by the Global Drug Survey in 2013/2014, I was unable to capture "dabbing", which uses concentrates (also known as Butane Hash Oil, 710, wax, shatter, dabs, glass), which are one of the most potent types of cannabis product available, often reaching 70% THC (Raber et al. 2015). Furthermore, vapes, edibles and concentrates are now are much larger part of the recreational cannabis market in the US (Light et al. 2014) and each hold unique risks and benefits that I was unable to consider in this thesis.

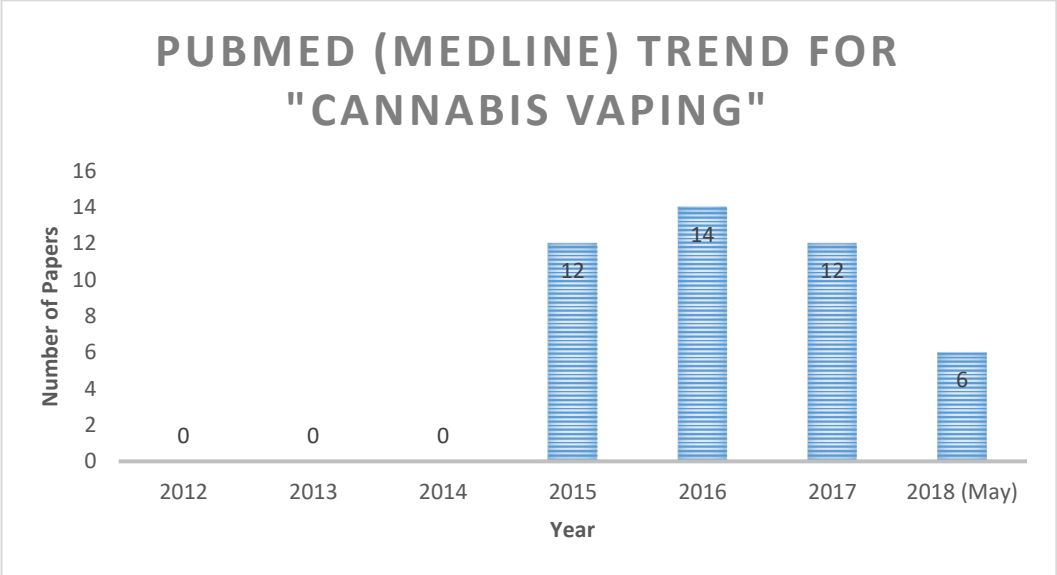


Figure 8.1. Bar chart representing the number of papers indexed by PuBMed published each year using the search term "cannabis vaping". Graph made with help from http://dan.corlan.net/medline-trend.html

The growth of vaping has been considerable. In 2017, Monitoring The Future reported that 10% of 12th graders (17-18 years old) had vaped cannabis in the past 12 months. Given that the overall levels of vaping among recreational drug users in chapter 2 was 11% in the US (and with Monitoring the Future estimating it at only 20%-25% for lifetime use in 2017), this is becoming a major issue in the US. I chose joints with tobacco, as they are still the most common ROA.

Moving away from combined use, via the use of vaping and edibles may be a way of global tobacco control. This is because they have the potential to dissociate cannabis from tobacco. However, vaping and edibles also have potential to change the pharmacokinetics and pharmacodynamics of THC and impact the overall amount of cannabis used – which may not necessarily lead to overall good. For example, in chapter 2, I found that people who vaped cannabis self-reported consuming more grams of cannabis compared with people using other non-tobacco routes (e.g. pipes, bongs, and joints without tobacco). This growing heterogeneity, which is similar to that seen for tobacco in the past (King et al. 2012), is a challenge for researchers. For example, it may mean that biological markers used to assess cannabis use which

depend on the pharmacokinetics of that form of administration, therefore making acute biomarkers less reliable e.g., drug driving breath tests will capture smoked cannabis but not edible cannabis.

In my opinion, the use of novel ROAs is directly related to another issue about the public perception of cannabis versus tobacco. The (American) public perception of cannabis as harmful is falling among adolescents in the United States (Monitoring the Future 2016), the use of cannabis has become more socially acceptable, and epidemiological data suggests there is an inverse relationship between perception of harm and the use of cannabis (Piontek et al. 2013). On the other hand, the perception of tobacco as harmful has increased (Cummings and Proctor 2014). Thus, with the increase in novel cannabis routes, a decrease in tobacco use, the population of co-users need to be considered as a hard-to-reach tobacco using population that require specialist tobacco cessation interventions. Emerging evidence suggests that the decrease in tobacco smoking worldwide may be hindered by medical marijuana laws. In a recent study, Wang et al. (2016) found that there was a higher proportion of co-users in states where medical marijuana was legal compared to illegal. Further, co-use was associated with higher odds for nicotine dependence than cigarette only use – this disproportionally effected young people. However, it should be noted that the data used in Wang et al. (2016) was from the 2013 NSDUH and is cross-sectional. Additionally, there is evidence that edibles and non-inhaled routes are increasing (Borodovsky et al. 2016). Therefore, only time will tell how legalisation will affect the way that people use cannabis. However, given the data I provide in chapter 2, this increase in tobacco use may indicate a larger problem for European countries aiming to liberalise their cannabis laws.

“Paralleling the diversification of cannabis products, there has also been a diversification of tobacco and nicotine delivery products. Indeed, even Phillip Morris has published advertisements suggesting they are “quitting cigarettes” (Malone 2018). By which they mean they are diversifying its nicotine delivery products away from

combusted cigarettes to products such as IQOS, which is a heat-not-burn product that may potentially be less risky than smoking. Electronic Nicotine Delivery Devices and vaporisation technology is also diversifying, all with the aim to reduce harm from smoking (McNeill et al. 2018). Finally, the products for cannabis and for nicotine are beginning to overlap – preliminary evidence suggests the use of cannabis via Electronic Nicotine Delivery Systems in young adults (Knapp et al. 2018)".

8.2.3 Measurement problems

"If you can't measure it, you can't manage it." Peter Drucker

The acute cannabis literature is undergoing a "measurement crisis" which can be considered part of the more general problem in psychology i.e. the "replication crisis". Quantifying cannabis and tobacco both biologically and through self-report needs to be considered carefully in study designs. However, variations in measures has led to methodical inconsistencies making it difficult to compare. The reluctance to, at least, report these important measures (as discussed in section 1.3.7), has implications for monitoring prevalence rates. For example, the European School Survey Project on Alcohol and other drugs (ESPAD) still asks about cannabis and tobacco separately and do not note it as a limitation (Kraus et al. 2018).

I explored how much cannabis and tobacco goes into a joint, and how this is affected by actually smoking cannabis and/or tobacco in chapter 5. Some researchers treat all "joints" equally or ignore quantity and focus on frequency of use. However, clearly joints vary in size, potency, and the number of people sharing. As such two people who smoke one joint per day are unlikely to consume the same amount of THC, and their consumption will differ from someone who smokes 10 joints a day. Failure to acknowledge these differences prohibits the establishment of clear definitions for problematic cannabis use and hinders our ability to make public health recommendations on using cannabis safely.

One way to solve this is to develop a “standard cannabis unit” (SCU) which I discussed in chapter 5 and a corresponding letter (“Solving the problem of cannabis quantification; Hindocha et al. (2018)). The SCU may allow for the development of low risk cannabis use guidelines similar to low risk alcohol use guidelines (Kalinowski and Humphreys 2016). This might be a measure of grams of THC; a direct measure of potency parallel to grams of ethanol in the standard alcohol unit. Just as individuals report the number of shots, bottles/pints of beer and glasses of wine, a similar measure would exist for cannabis e.g. one joint with high potency cannabis versus one joint with low potency hashish. The reason this is necessary is because recreational cannabis users find it very difficult to estimate grams of cannabis as well as cannabis potency (Chapter 5; (Freeman et al. 2014b)). Indeed, recently a paper reported that utilising the Roll a Joint paradigm developed in chapter 5 accounts for more variance in cannabinoid biomarkers (urinary THC) in comparison to frequency alone and number of joints per day (a simpler measure of quantity) (Tomko et al. 2018). A combination of quantity and potency are needed to develop the SCU. Accounting for this variation in dose of THC and CBD may help differentiate users at high versus low risk for problematic use. For example one standard cannabis unit may be equivalent to 0.25g of High THC/Low CBD cannabis=0.5g of cannabis with equal THC/CBD=0.75g of Low THC/High CBD cannabis). This would be the equivalent to current standard alcohol unit measures: 1 standard drink unit=12 oz beer=5 oz wine=1.5 oz of 40% alcohol spirit.

Another way to approach this measurement problem is to investigate the most sensitive cognitive, self-report and biological metrics for reporting cannabis use. Once this consensus has been achieved, an online toolkit such as the consensus measures for **Phen**otypes and e**X**posures (PhenX) toolkit can be used (https://www.phenxtoolkit.org). The PhenX Toolkit catalogues recommended and standardised measures for biomedical research. It and can be used to expand study designs and analyse studies across measures. The PhenX Toolkit is a web-based

resource and is available for use at no cost. In my lab, we have begun investigation into the best self-report and biological metrics of cannabis use (Curran et al. submitted).

Finally, although asking participants to report their own quantity and frequency retrospectively is the most cost-effective measure it is limited by memory and the difficulty of estimating cannabis (chapter 5; Freeman et al. 2014b). The most commonly used measure is the timeline follow-back method, which aids recall. Novel technologies can now be used to better assess drug use; measures such as ecological momentary assessment that require participants to log every drug use, and can include pictures and assessments of cognition are now being utilised. Additionally, armbands and ankle bracelets can track bodily fluids and heart rate to provide continuous estimates of biological markers.

8.3 Strengths and limitations

Strengths and limitations have been discussed specifically for each chapter and therefore only general strengths and limitations are discussed here.

One major strength of this thesis is the use of randomised, within-subjects placebo-controlled crossover designs. The advantage of such a design is that each participant serves as his or her own control and this significantly reduces between-subject variability, allowing the detection of smaller effect sizes with reduced sample sizes. Therefore, making these studies economical in both time and money. Additionally we used power calculations in each study to ensure the right about of participants and increased the sample to account for the winners curse.

I would also like to address the problem of experimental specificity. In chapter 2, I used a study of over 30,000 cannabis users (with at least one use of cannabis in the past year) who had varying levels of tobacco use (both in combined use and concurrent use). I also recruited a sample of 24 non-dependent cannabis and tobacco co-users, and 30 cigarette dependent, non-cannabis users. This different choice of participants as well as doses of drug, regimes and history, and routes of administration need to be

taken into account when interpreting the results of this thesis. One example of this is that in studies 3, 4 and 5, I used non-dependent users because I did not want the effects of dependence to interact with the investigation of the subtle pharmacological and behavioural changes that may have occurred with tobacco, however, this limits my ability to speak to addiction of co-used cannabis and tobacco.

The dose of cannabis and tobacco used was not weight adjusted and I did not have a limit on this, therefore future studies should weight-adjust the dose of cannabis used. I have also discussed problems with dosing of CBD – although I do not consider this a limitation.

One further limitation is the relative lack of attention paid to self-reported alcohol use. In these studies, I did not use an objective marker of alcohol use to exclude participants e.g. breathe alcohol levels.

Finally, I am not justified to using the terms nicotine and tobacco interchangeably in this thesis as they are not interchangeable, in that nicotine is not the only primary psychoactive component of tobacco (and nicotine delivery (dose, speed etc) will vary depending on how the tobacco is consumed (e.g. combusted or not combusted). Furthermore, throughout I have been using a CO measure throughout to assess recent tobacco use, but participants may have been vaping nicotine through an e-cigarette, which would not be evidenced via a CO measure. Additionally, in chapter 2, tobacco and non-tobacco routes are separated by the use of tobacco itself, however in chapters 3-5, we use a denicotinized tobacco to maintain the blinding of the study and as such I was manipulating nicotine only, but there are also non-nicotinic components that drive addiction (Benowitz 2010) and non-nicotine components are psychoactive (Lewis et al. 2007).

8.4 Implications and future thinking

These findings are important clinically. As the prevalence of co-use of cannabis and tobacco is so large, and there is huge public health momentum in reducing rates of

smoking tobacco as evidenced by the implementation of the Framework Convention of Tobacco control (WHO, 2003). However, when an individual goes to their Stop Smoking Service or their GP, healthcare practitioners are often unaware of additional tobacco exposure as a function of cannabis use, because of individual's co-use that may be preventing them from giving up smoking. This is concerning, given that this likely reflects a substantial proportion of people with cannabis problems in Europe. Although this tobacco use might not necessarily reflect clients' primary concern (and may go unreported), I suggest that clinicians should routinely ask about cannabis, when assessing tobacco-related problems, and vice versa. Unfortunately, there is little evidence-based advice that one can give to cannabis users who wish to give up tobacco. Therefore we need to develop effective interventions and test whether existing theoretical frameworks such as the Behaviour Change Wheel are relevant for characterising co-use and assisting dual quit attempts (Walsh et al. 2017).

From a public health perspective, tobacco should play an important role in conversations about cannabis policy, which are occurring at a faster pace now than ever before. This is especially the case in Europe where the likelihood of smoking cannabis *without* tobacco is minimal. Policy changes focusing on cannabis could have a considerable impact on tobacco use and smoking cessation services, and therefore should be adapted with this consideration in mind. Health promotion campaigns should aim to dissociate the use of cannabis and tobacco, especially in young people – for whom this may be their first, only, and largely preventable gateway to tobacco addiction (Hindocha et al. 2016b). Table 8.2 summarises the results and implications derived from this thesis and was originally published along with chapter 2 (Hindocha et al. 2016a) but has been updated to incorporate the results from this thesis. It also summarises future directions for research.

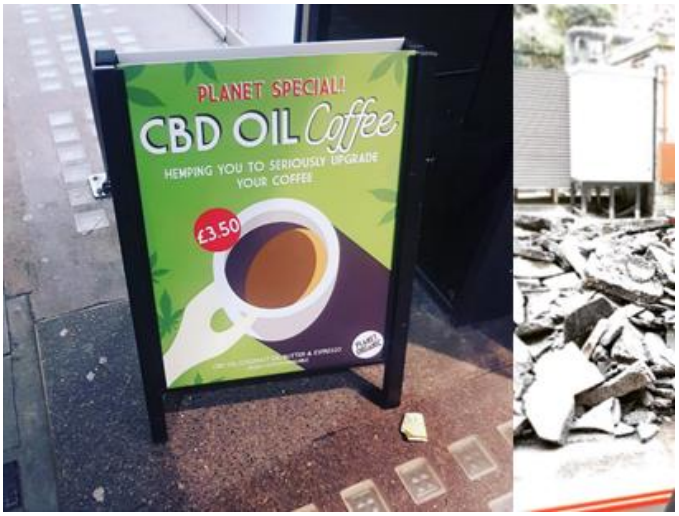
Table 8.2. Summary of results, implications and future directions for reducing and preventing cannabis and tobacco co-use future directions

Strategy	Evidence-base + Implications
Dissociate tobacco from cannabis	• Combining cannabis and tobacco together does not influence the rewarding effects of cannabis (chapter 3/4) and makes individuals less likely to want to quit tobacco (chapter 3) • Combining cannabis and tobacco leads to poorer cardiovascular health acutely (chapter 3) • Public health messaging should explain lack of benefit from tobacco is minimal in regards to pleasure and harms to cardiovascular health
Promote alternative ROAs such as vaporizers	• Vaporizers may be an acceptable harm reduction intervention to promote due to less damage on the respiratory system (Van Dam and Earleywine, 2010) • Moving away from combusted cannabis products may be a way of improving global tobacco control • Vaping cannabis has the potential to reduce both cannabis-related pulmonary harms and tobacco addiction (Hindocha et al. 2016)
Clinical Training	• Stop smoking services should be aware of role of combined cannabis and tobacco use in the addiction cycle and aim to target both for dual cessation. • Alternatively, administering cannabis without tobacco may increase motivation to change tobacco use
Account for the use of combined cannabis and tobacco in psychosis research	• Epidemiological evidence suggests both cannabis and tobacco are independent risk factors for psychosis • Nicotine did not modulate cannabis induced psychotic-like symptoms in healthy controls (Chapter 3). This does not negate the causal role of tobacco in psychosis and future research is required within a psychotic population • Properly delineating tobacco from cannabis in epidemiological research is essential • Given the regional variation of co-use, a comparison of psychosis rates across the world based on co-use levels would be an interesting avenue.
Investigation of Cannabidiol for problematic co-use/dual disorders	• Current medications for cigarette smoking do not produce high rates of smoking abstinence, and many cigarette smokers find themselves in a cycle of addiction • Novel medications such as CBD for smoking cessation need to be further investigated in randomised control trials, imminently. If positive then CBD should investigated for combined CUD and TUD • Investigation of CBD for both tobacco smoking and psychosis, given a potential shared biological underpinning of disrupted salience attribution.
Accounting for regional variation	• Administering cannabis with tobacco is most common in Europe (chapter 2) • As cannabis policy becomes more liberalized, dialogue between policies to reduce tobacco smoking and those regarding cannabis will be necessary to ensure no delay in global tobacco control
Future directions	
Vaporizers	• Further research is required be better define the harm reduction benefits of vaporizers on respiratory health and function as well as potential harms associated with vaporizer use

Harm reduction	• Health promotion campaigns should focus on dissociating the use of tobacco and cannabis and should consider differential harm reduction campaigns for cannabis users who use cannabis with tobacco
Monitoring and Measurement	• A more accurate description of how cannabis is consumed worldwide through better monitoring and screening tools is fundamental. Household surveys in adults and youth should be capturing changing cannabis and tobacco based behaviors across the world • Utilizing the "roll a joint paradigm" in experimental and observational research will increase the accuracy of cannabis and tobacco measurement – allowing a better understand of the risks of combined use
Controlled Experimental Studies	• Investigating the role of nicotine in establishing and maintaining CUDs and vice versa. Does the cannabinoid content (THC: CBD ratio influence the relationship between cannabis and tobacco • Establish whether co-use plays a causal role in maintaining addiction
Observational research	• A large online sample of co-users who vary in cannabis/THC and tobacco/nicotine exposure, then utilise a cluster analysis to reveal the underlying latent classes and using the classes to predict long-term outcomes

8.5 My PhD Journey

In the short period (2015-2018) that I have been working towards the completion of my PhD, there have been rapid changes in cannabis use. Full CB1 agonists, often referred to as Spice or K2, have become worryingly prevalent, and pose far more danger to users than natural cannabis (Winstock et al. 2015; Winstock and Barratt 2013) and novel routes and combinations of routes have appeared. At the same time, a booming cannabis industry continues to emerge, with some sources suggesting that it will be a



$22 billion industry by 2021 (ArcView Market Research, 2017). CBD has become the centre of a novel “nutraceutical” and wellness industry; posited by online sources to cure every ailment and being used in coffee (see below). This has been simultaneous to the first CBD-based medication, called Epidiolex (GW Pharmaceuticals), being licenced by the FDA for its use in childhood epilepsy (Kaplan 2018).

As I write this, the UK is in the midst of potentially groundbreaking change in British Law. The Home Secretary has announced a review of medicinal cannabis such that it may be moved from a Schedule 1 drug, with no approved medical uses, to Schedule 2, with acknowledged medical uses (legal medical cannabis will be available in the UK on November 1st 2018). Drugs in Schedule 2 and 3, such as methadone, can be prescribed by doctors and supplied by a pharmacist. Under the current Schedule 1, conducting research with such drugs is a considerable hurdle to face. My own specific example of this is portrayed above. In 2015/2016, the future of my cannabis-tobacco interaction study was in jeopardy when I had to stop testing for my study as I discovered that overnight the carpark had been uplifted (the only designated area I could use to administer joints). I had nowhere to go to give my participants their joints that was not “in public view” and therefore against the conditions of our Home Office Licence. Thankfully, after a few weeks, we were able to confirm another designated area.

In the same week that the UK announced this review of medical cannabis, Canada passed The Cannabis Act, legalising recreational cannabis, to be available as early as October 2018.

Doubtless, to say, there will be exciting times ahead for cannabis!

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APPENDIX A

Ethics Approval - Chapter 2

NHS
Health Research Authority

NRES Committee London - Camberwell St Giles

[redacted]

11 October 2013

Dr Adam R Winstock

[redacted]

Dear Dr Winstock

Study title:	**Mixmag Annual Drug Survey**
REC reference:	**141/02**
Amendment number:	**Substantial Amendment 8,17.08.13**
Amendment date:	**01 October 2013**
IRAS project ID:	

The above amendment was reviewed at the meeting of the Sub-Committee held in correspondence.

Ethical opinion

There were no outstanding ethical issues.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Questionnaire: S1 HRLSDMUS	8	01 October 2013
Questionnaire: S4 NO	8	01 August 2013
Notice of Substantial Amendment (non-CTIMPs)		01 October 2013
Questionnaire: S2 CANNABIS	8	01 August 2013
Questionnaire: S1 HRKET	8	01 August 2013
Questionnaire: S5 SILK ROAD	8	01 August 2013
Letter from Sponsor		01 October 2013
Questionnaire: S1 HRBHG	8	01 August 2013

Covering Letter		01 October 2013
Questionnaire: S7 POLICY	8	01 August 2013
Questionnaire: S1 HRSTIM	8	01 August 2013
Questionnaire: S3 WORKPLACE	8	01 August 2013
Questionnaire: S1 HRTOBAC	8	01 August 2013
Questionnaire: S6 PRESCRIPTION	8	01 August 2013
Questionnaire: S1 HRMDMA	8	01 August 2013

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

141/02:	**Please quote this number on all correspondence**

Yours sincerely

[redacted]

Enclosures: *List of names and professions of members who took part in the review*

APPENDIX B

Ethics approval – Chapter 3, 4 and 5

UCL RESEARCH ETHICS COMMITTEE
ACADEMIC SERVICES

29 January 2016

Professor Valerie Curran
Research Department of Clinical, Educational and Health Psychology

Dear Professor Curran

Notification of Ethical Approval
Project ID: 7725/001: How does nicotine influence the subjective, cognitive and physiological effects of cannabis?

I am pleased to confirm in my capacity as Chair of the UCL Research Ethics Committee that I have approved your study for the duration of the project until September 2018.

Approval is subject to the following conditions:

1. You must seek Chair's approval for proposed amendments to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the 'Amendment Approval Request Form': http://ethics.grad.ucl.ac.uk/responsibilities.php

2. It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator (ethics@ucl.ac.uk) immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an independent expert. The adverse event will be considered at the next Committee meeting and a decision will be made on the need to change the information leaflet and/or study protocol.

   For non-serious adverse events the Chair or Vice-Chair of the Ethics Committee should again be notified via the Ethics Committee Administrator (ethics@ucl.ac.uk) within ten days of an adverse incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

On completion of the research you must submit a brief report of your findings/concluding comments to the Committee, which includes in particular issues relating to the ethical implications of the research.

Yours sincerely

[redacted]

Professor John Foreman
Chair of the UCL Research Ethics Committee

[redacted]

UCL RESEARCH ETHICS COMMITTEE

Amendment Approval Request Form

1	**Project ID Number:** 7725/001	**Name and Address of Principal Investigator:** Professor H Valerie Curran [redacted]
2	**Project Title:** : How does nicotine influence the subjective, cognitive and physiological effects of cannabis?	
3	**Type of Amendment/s (tick as appropriate)** ☒ Research procedure/protocol (including research instruments) ☐ Participant group ☐ Sponsorship/collaborators ☐ Extension to approval needed (extensions are given for one year) ☒ Information Sheet/s ☐ Consent form/s ☐ Other recruitment documents ☐ Principal researcher/medical supervisor* ☐ Other * *Additions to the research team other than the principal researcher, student supervisor and medical supervisor do not need to be submitted as amendments but a complete list should be available upon request.	
4	**Justification** (give the reasons why the amendment/s are needed) Following a pilot study, we have found that the amount of tobacco used in this study needs adjusting in two ways. First, we need to slightly increase the amount of tobacco from a quarter of a cigarette (155mg) to half a cigarette (311mg). This is more realistic to naturalistic cannabis-tobacco use and is well within the normal range of what cannabis users would use. Secondly to make the amount of material ingested more controlled, we need to add half of the placebo cigarette (311mg) to each cannabis-tobacco prepared cigarette. This would not be smoked but simply be used as placebo filler in the base of the prepared cigarette. Participants will then smoke to a predefined line where the placebo filler begins. Participants thus only smoke the top half of the prepared cigarette. Due to the natural variation in the growing and production of cannabis, the release specification of the medicinal cannabis we imported from Holland gives the dosage as 16.1% THC and we would like to update the committee on this issue (the original application stated 12%). This is within the normal variation in cannabis potency found in the UK (Hardwick & King, 2008).	
5	**Details of Amendments** (provide full details of each amendment requested, state where the changes have been made and attach all amended and new documentation) 1. An increase in active/placebo tobacco in the study drug proportion of the cannabis-tobacco prepared cigarette. As explained in the full ethics application we were initally going to use a quarter of a cigarette, and now we will use half a cigarette. This has been updated on the information sheet. 2. The addition of placebo (non-nicotine tobacco) to the base of each prepared cigarette to make it more comfortable for the participant to smoke. 3. The %THC of the cannabis has changed from 12% to 16.1%.	
6	**Ethical Considerations** (insert details of any ethical issues raised by the proposed amendment/s) We do not think that these amendments to procedure raise any ethical implications. Participants all have experience smoking cannabis and tobacco together. The amount of tobacco is inceasing but participants will be used to smoking this amount of tobacco with their own cannabis and this is well within the normal range of tobacco used within prepared cigarettes. The cannabis has increased in potency, but this is	

	should not be an issue, as it is closer to the potency of the street-cannabis that participants will have experience smoking, and again, well within the normal range.
7	**Other Information** (provide any other information which you believe should be taken into account during ethical review of the proposed changes)

Declaration (to be signed by the Principal Researcher)

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendments to be implemented.
- For student projects I confirm that my supervisor has approved my proposed modifications.

Signature:

[redacted]

Date: 01/03/2016

FOR OFFICE USE ONLY:

Amendments to the proposed protocol have been Approved by the Research Ethics Committee.

Signature of the REC Chair, Professor John Foreman: [redacted]

Date: 04/03/2016

CLINICAL PSYCHOPHARMACOLOGY UNIT

Information Sheet for Voluntary Participants in Research Studies

You will be given a copy of this information sheet.

Title of Project: **How does nicotine influence the subjective, cognitive and physiological effects of cannabis?**

This study has been approved by the UCL Research Ethics Committee (Project ID Number): 7725/001

Name: Professor H Valerie Curran

Work Address [redacted]

Contact Details Telephone: [redacted]

We would like to invite cannabis and tobacco users to participate in this research project.

Details of Study:

You are being invited to take part in a research study. Before you decide whether to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?

Most people who use cannabis tend to use tobacco at the same time. This study aims to increase our understanding of why people use cannabis and tobacco together. We want to understand what effect this has on how people think and feel after they have used cannabis and/or tobacco. This study is being conducted by researchers from the Clinical Psychopharmacology Unit at University College London. Before we describe the study and its purpose we would like to make it clear that this is a *completely voluntary study* and that you will be free to pull out at any time.

Do I have to take part?

It is up to you whether or not to take part. If you decide to do so, you will be asked to sign a consent form but are still free to withdraw at any point without giving the researcher a reason.

What will happen to me if I take part?

If you decide to take part, you will be asked to attend four testing sessions, each lasting about 1.5 hours. The first session will be slightly longer than the rest, and this will be used to collect information about your general health and wellbeing. Each of the testing sessions will be around 7 days apart. **All volunteers must agree to not use any recreational drugs (including cannabis), alcohol or tobacco from at least 12 hours before each test day, and this will be tested with a saliva sample and a breath sample.** Females will also be tested for pregnancy via a urine sample on each test day. If your test results suggest that you have used recreational drugs in the last 12 hours, or that you might be pregnant, **you will not be permitted to take part**.

On each test day you will be asked to fill out questionnaires about your mood and mental state. You will then be asked to inhale one of four combinations of drugs via a pre-prepared cigarette. These 4 combinations are made up of normal cannabis and tobacco and 'inactive' (placebo) cannabis and inactive tobacco.

1) Cannabis + tobacco
2) Cannabis + inactive tobacco
3) Inactive cannabis + tobacco
4) Inactive cannabis + inactive tobacco

You will receive each of these combinations across the four test days. The dose of cannabis you will receive is similar to a small 'recreational' dose (8mg THC). The dose of tobacco you will receive is 0.8mg nicotine (this is about 1/2 of a cigarette and equivalent to what people normally put into a joint when they smoke cannabis and tobacco).

You will be asked to fill out some further questionnaires about your mood and mental state and do some computer tasks. On each test day we will record your blood pressure, heart rate, and collect samples of saliva. These samples will be labelled anonymously and stored securely at -80°C. They will be sent for analysis of THC and cotinine (to measure cannabis and tobacco use). Afterwards, these samples will be destroyed.

Each test day will last for about 1.5hours. Most people find the tests quite straightforward and fun to do. Neither you nor the researcher will know on which day you will receive each combination of cannabis and tobacco (the study is **double-blind**). **You should not drive or operate machinery on any of the test days**, even if you think don't think you received any active drug.

If you agree to take part you will also be asked whether you are happy to be contacted about participation in future related studies. Your participation in the present study will not be affected should you choose to be re-contacted or not.

What are the risks of taking part in this study?

The dose of cannabis will be in similar or lower quantities than those commonly used 'recreationally' with street cannabis. As participants are all experienced cannabis and tobacco users, no risks are envisaged from the administration of either cannabis or tobacco. You should be familiar with its effects, which include feeling 'stoned', hungry and giggly. A medical doctor will be available in the unlikely event of you experiencing problems during the study.

What are the benefits to me?

You will leave with the knowledge that you have contributed to our understanding of the effects of cannabis and tobacco. In addition, you will be given a one page summary of results when the study has finished and an information leaflet containing advice for stopping cannabis use.

Will I receive compensation for giving my time?

You will be given a small honorarium of just over £9 per hour to compensate you for your time.

How will my data be kept?

Your data from this study will be stored electronically using a numbered code so that you cannot be personally identified. Only researchers directly involved in the study have access to the data. All data will be collected and stored in accordance with the Data Protection Act (1998).

Who is organising and funding the research?

The study is organised by the Clinical Psychopharmacology Unit at UCL and is funded by the Medical Research Council.

Who has reviewed the study?

The study has been review by the UCL Research Ethics Committee

Subject Rights and Study Withdrawal

Participation in research is entirely voluntary. You may refuse to participate or withdraw **at any time**.

Your participation in this study may be ended <u>without</u> your consent if:

1. the investigator believes that it is in your best interest
2. the project is terminated
3. you no longer meet study criteria

Who can I contact for further information?

If you have any further questions please contact:

Chandni Hindocha

Prof. H. Valerie Curran

[redacted]

APPENDIX C

Ethics approval – Chapters 6 and 7

UCL RESEARCH ETHICS COMMITTEE
ACADEMIC SERVICES

29th November 2016

Professor Valerie Curran
Research Department of Clinical, Educational and Health Psychology
UCL

Dear Professor Curran

Notification of Ethical Approval
Re: Ethics Application 7725/002: Modulating the endocannabinoid system using cannabidiol (CBD) to investigate nicotine withdrawal in dependent cigarette smokers

I am pleased to confirm in my capacity as Chair of the UCL Research Ethics Committee (REC) that your study has been ethically approved by the REC until **28th August 2018** on condition that the UCL Sponsor Pharmacist's risk minimisation measures outlined in the attached letter are taken into consideration. There were no major issues, except that the dose made is 50mg, so participants have to take 16 capsules to make up 800mg and this should be made clear in the Participant Information Sheet.

Approval is also subject to the following conditions:

Notification of Amendments to the Research
You must seek Chair's approval for proposed amendments (to include extensions to the duration of the project) to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the 'Amendment Approval Request Form':
http://ethics.grad.ucl.ac.uk/responsibilities.php

Adverse Event Reporting – Serious and Non-Serious
It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator (ethics@ucl.ac.uk) immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an independent expert. For non-serious adverse events the Chair or Vice-Chair of the Ethics Committee should again be notified via the Ethics Committee Administrator within ten days of the incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

Final Report
At the end of the data collection element of your research we ask that you submit a very brief report (1-2 paragraphs will suffice) which includes in particular issues relating to the ethical implications of the research i.e. issues obtaining consent, participants withdrawing from the research, confidentiality, protection of participants from physical and mental harm etc.

[redacted]

Yours sincerely

[redacted]

Professor John Foreman
Chair, UCL Research Ethics Committee

Enc. Letter from Anna Song, Regulatory Manager – Pharmaceuticals

Cc: Chandni Hindocha

University College London Hospitals NHS
NHS Foundation Trust
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Joint Research Office

[redacted]

Re: Modulating the endocannabinoid system: does cannabidiol (CBD) affect the severity of nicotine withdrawal symptoms in non-treatment seeking dependent cigarette smokers?
(Prof. H. Valerie Curran, Ethics ID: 7725/002)

The purpose of this document is to assess the use of **cannabidiol 50mg capsules** and their **placebo** for use in the above referenced clinical study.

In order to assess the risk the following will be looked at:

1) The formulation quality and licensing status
2) The fitness for purpose
3) The management of the medicines

Formulation quality and the licensing status

Cannabidiol/placebo

Cannabidiol is an unlicensed formulation in the UK and will be obtained specifically for this study by STI pharmaceuticals and manufactured in a blinded fashion by Nova Labs under the manufacturing license number MIA(IMP) 13581 within EU GMP regulations. The capsules are size 2 red capsules containing 50mg cannibidiol or placebo. Placebo will be the same capsules but filled with lactose powder.

The quality of the materials will not be further investigated.

Fitness for purpose

Consideration needs to be given to the pharmacology (both pharmacokinetic and pharmacodynamics) of the investigational material in the formulation proposed for the study with respect to the study's intended use.

As proposed, cannabidiol works has a low affinity towards receptors CB1 and CB2 within the human endocannabinoid system (ECS). These receptors are predominantly at nerve terminals where they regulate synaptic function. Cannabidiol acts as a partial antagonist at both CB1 and CB2 receptors, to modulate effects of neurotransmitters. It is currently licensed in the UK as an oromucosal spray (Sativex®) with an indication in moderating spasticity in multiple sclerosis sufferers.

University College London Hospitals NHS
NHS Foundation Trust

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This study intends to investigate the effect of cannabidiol on nicotine withdrawal symptoms as a single dose of 800mg (patients are to take 16 of 50mg capsule of cannabidiol/placebo).

There have been several studies using cannabidiol up to a maximum dose of 1500mg with minimal risk to patients. Cannabidiol has also been investigated in nicotine dependant participants in the form of an inhaler, with results indicating a reduction in cigarettes smoked within the active group.

The study and its research use so far have shown cannabidiol to have a favourable safety, tolerability and pharmacokinetic profile.

Management of the medicines

Blinding arrangements: This study will be double-blinded. Patients will be randomised using a computer algorithm for treatment assignment to avoid bias and ensure event distribution of treatment. The randomised patient will receive a treatment number and kit specific code to ensure the correct treatment is dispensed to the patient. Treatment is packaged in coded envelopes which the investigator will hand out as per patient visit date.

The investigator will have access for unblinding codes for use in scenarios of unblinding.

Study medicines sourcing and accountability arrangement: As a measure of risk minimisation it is suggested -

1. Patients should be made aware (not clear from PIS/protocol) that they are to take 16 capsules in one go in order to obtain 800mg cannabidiol.
2. Drugs should be clearly segregated from other stock to facilitate management and stored at temperature ranges as specified by supplier. It is recommended that as a minimum a calibrated min/max thermometer is used to record storage temperatures.
3. Cannabidiol/placebo should be dispensed as per valid prescription and per patient randomisation.
4. Accountability logs should be maintained to allow traceability of medication, especially in cases of unblinding or adverse events.

18th November 2016

[redacted]

Anna Song
Regulatory Manager - Pharmaceuticals

UCL RESEARCH ETHICS COMMITTEE

Amendment Approval Request Form

1	**Project ID Number:** 7725/002	**Name and Address of Principal Investigator:** Professor H Valerie Curran [redacted]
2	**Project Title:** Modulating the endocannabinoid system using cannabidiol (CBD) to investigate nicotine withdrawal in dependent cigarette smokers.	
3	**Type of Amendment/s (tick as appropriate)** ☒ Research procedure/protocol (including research instruments) ☐ Participant group ☐ Sponsorship/collaborators ☐ Extension to approval needed (extensions are given for one year) ☒ Information Sheet/s ☐ Consent form/s ☐ Other recruitment documents ☐ Principal researcher/medical supervisor* ☐ Other * *Additions to the research team other than the principal researcher, student supervisor and medical supervisor do not need to be submitted as amendments but a complete list should be available upon request.	
4	**Justification** (give the reasons why the amendment/s are needed) 1. We have changed participant compensation from £7.50 per hour to £10 per hour to come into line with other studies of this kind, and abide by departmental rates for participant compensation. We believe this is more appropriate for an abstinence study. 2. We have added to the information sheet that participants will be given 16 capsules at the request of UCL pharmacy. 3. We have added a rewards task into the study and therefore amended the telephone screener to ask participants if they are allergic to chocolate and to name three songs that they like.	
5	**Details of Amendments** (provide full details of each amendment requested, state where the changes have been made and attach all amended and new documentation) 1. Compensation. We have made this change to the information sheet to reflect departmental compensation rates. Moreover, remaining abstinent twice for 12 hours is a commitment, and therefore we have increased this payment rate. 2. Drug administration. As requested by UCL pharmacy (see 7725.002 Sponser Pharmaceutical Review Letter), we have included in the information sheet that participants will be given 16 capsules with a glass of water. This will allow participants, who do not wish to swallow 16 capsules, to have the correct information and the option to not take part, as they wish. 3. Rewards task: This task asks participants how much they want a piece of chocolate/a minute of their preferred music/£2 to keep/a cigarette, followed by actual 'consumption' of these rewards i.e. to eat the chocolate/listen to the music/hold the £2 (and smoke a cigarette - which was already in the procedure), followed by rating how much they liked these reward. As a result of adding this task, we have modified the telephone screener to ask participants if they are allergic to chocolate and to provide three songs they like.	

6	**Ethical Considerations** (insert details of any ethical issues raised by the proposed amendment/s) We do not think these amedments to procedure raise any ethical implications.
7	**Other Information** (provide any other information which you believe should be taken into account during ethical review of the proposed changes)

Declaration (to be signed by the Principal Researcher)

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendments to be implemented.
- For student projects I confirm that my supervisor has approved my proposed modifications.

Signature: [redacted]

Date: 16/01/2016

FOR OFFICE USE ONLY:

Amendments to the proposed protocol have been approved by the Research Ethics Committee.

Signature of the REC Chair, Professo [redacted]

Date: 18/1/2017.

Version 2

INFORMATION SHEET

CLINICAL PSYCHOPHARMACOLOGY UNIT

Information Sheet for Voluntary Participants in Research Studies

You will be given a copy of this information sheet.

Title of Project: **Modulating the endocannabinoid system using cannabidiol (CBD) to investigate nicotine withdrawal in dependent cigarette smokers**

This study has been approved by the UCL Research Ethics Committee (Project ID Number): 7725/002

[redacted]

We would like to invite cigarette smokers to participate in this research project.

Details of Study:

You are being invited to take part in a research study. Before you decide whether to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?

Many people are addicted to cigarettes and find it difficult to stop smoking. Current treatments to help people quit are not very effective in the long term. When people do stop they experience withdrawal which are unpleasant symptoms that often make people relapse. This study aims to see if a drug called cannabidiol or CBD can help with these withdrawal symptoms. This study is being conducted by researchers from the Clinical Psychopharmacology Unit at University College London. Before we describe the study and its purpose we would like to make it clear that this is a *completely voluntary study* and that you will be free to pull out at any time.

What is Cannabidiol (CBD)?

Cannabidiol is a natural substance that is found in cannabis. Many people have heard of the other component of cannabis called THC which makes people stoned. CBD, on the other had has opposite psychological and pharmacological effects, and does not make you feel stoned. CBD is not a licenced medicine.

Do I have to take part?

It is up to you whether or not to take part. If you decide to do so, you will be asked to sign a consent form but are still free to withdraw at any point without giving the researcher a reason. If you do take part, you will contribute to the scientific knowledge of tobacco addiction ad help us with the development of better treatments.

Why have I been invited?

Version 2

You have been invited to take part as you have expressed an interest in the study and you are a dependent cigarette smoker.

What will happen to me if I take part?

If you are interested in taking part, please email us on smokingstudy2017@gmail.com with a phone number and good time to call, then we will call you (10 mins max) and ask you some questions to see if you are eligible.

If you are eligible you will be asked to attend THREE testing sessions. In the first session, you will be asked to come to the Clinical Psychopharmacology Unit at UCL where you will just *smoke as normal*. We will ask for a urine sample to ensure you have not recently used illicit drugs, including cannabis. If your urine test is positive for drugs then you will not be able to take part. Afterwards, these urine samples will be destroyed. Females will undergo a pregnancy test. You will then be asked to do some straightforward pen/paper and computer tasks.

For the next two sessions you must *not smoke cigarettes for the 12 hours* before the session. We understand this can be difficult but if you ever decide to quit in the future it will be good to know that you not smoke for a 12-hour period. On these days we will check the carbon monoxide in your breath to check that you have not smoked. If you have smoked, we will not be able to continue with the session and we will have to rearrange. You will then be given either 800mg CBD or placebo. This will be taken via 16 individual capsules with a glass of water. Neither you nor the experimenter will know which drug you get when (the study is **double-blind**). *There will be a waiting period of 2.5 hours - please bring a book/laptop to work on/read - you will not be allowed to smoke during this time*. After this waiting period, you will again be given some pen/paper and computer tasks. At the end of each of these sessions, you will smoke a cigarette through a device that measures the depth of your inhalations.

The most important part is that you do not smoke for the 12 hours before the session. If the breathalyser test shows that you have been smoking, then we have to cancel the session and you will not be reimbursed for your time.

A short time after your final session we will call or email you and follow up with asking you about your smoking patterns and mood. There will be an additional reimbursement for this.

We estimate the first session will last 2 hours and the others will last 4 hours. Most people find the tests quite straightforward and fun to do. **You should not drive or operate machinery on the second or third test days**, even if you think didn't think you received any active drug.

If you agree to take part, you will also be asked whether you are happy to be contacted about participation in future related studies. Your participation in the present study will not be affected if you choose to be re-contacted or not.

What are the risks of taking part in this study?

The drug (CBD) has been tested in several previous studies and has been shown to be well tolerated in humans at 800mg. You might experience mild sedation (sleepiness) which others have experienced at this dose. We do not expect you experience other side effects. If you think that you are suffering from a side effect, you should let the experimenter know. A medical doctor will be available in the unlikely event of you experiencing problems during the study.

Most cigarette smokers find it hard to stay abstinent for 12 hours so you might experience withdrawal effects during this period such as irritability, headaches or craving.

What are the benefits to me?

You will leave with the knowledge that you have contributed to our understanding of the effects of tobacco addiction. In addition, you will be given a one page summary of results when the study has finished.

Version 2

Will I receive compensation for giving my time?

You will be given an honorarium of £10 per hour (£100.00 total at the end of the three sessions). An extra £5 will be paid if you complete a short assessment a week later.

How will my data be kept?

Your data from this study will be stored electronically using a numbered code so that you cannot be personally identified. Only researchers directly involved in the study have access to the data. All data will be collected and stored in accordance with the Data Protection Act (1998).

Who is organising and funding the research?

The study is organised by the Clinical Psychopharmacology Unit at UCL and is funded by the Medical Research Council.

Who has reviewed the study?

The study has been review by the UCL Research Ethics Committee

Subject Rights and Study Withdrawal

Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time. Your participation in this study may be ended without your consent if:

1. the investigator believes that it is in your best interest
2. the project is terminated
3. you no longer meet study criteria

Who can I contact for further information?

If you have any further questions please contact:

Chandni Hindocha

Prof. H. Valerie Curran [redacted]