Recreational stimulants, herbal and spice cannabis: the core psychobiological processes which underlie their damaging effects.

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Abstract.

Aims: recreational drugs are taken for their positive mood effects, yet their regular usage damages wellbeing. The psychobiological mechanisms underlying these damaging effects will be debated.

M*ethods:* the empirical literature on recreational cannabinoids and stimulant drugs will be briefly reviewed. A theoretical explanation for how they cause similar types of damage will be outlined.

Results. All psychoactive drugs cause moods and psychological states to fluctuate. The acute mood gains underlie their recreational usage, while the mood deficits on withdrawal explain their addictiveness. Cyclical mood changes are found with every CNS stimulant, and also occur with cannabis. These mood state changes provide a surface index for more profound psychobiological fluctuations. Homeostatic balance is altered, with repetitive disturbances of the HPA axis, and disrupted patterns of cortisol-neurohormonal secretion. Hence these drugs cause increased stress, disturbed sleep, neurocognitive impairments, altered brain activity, and psychiatric vulnerability. Equivalent deficits occur with novel psychoactive stimulants such as mephedrone, and artificial 'spice' cannabinoids. These psychobiological fluctuations underlie drug dependency, and make cessation difficult. Psychobiological stability and homeostatic balance are optimally restored by quitting psychoactive drugs.

Conclusions: recreational stimulants such as cocaine and sedative drugs like cannabis, damage human homeostasis and well-being through similar core psychobiological mechanisms.

Keywords: cannabis - amphetamine - MDMA - spice - cocaine - cognition

Introduction.

Current campaigns to decriminalize the use of cannabis for recreational purposes have portrayed it as a relatively benign substance. Proponents for cannabis suggest that it is a relaxant and euphoriant, which makes the user feel better, and everyone should be free to use it. For professionals working in the field of drug dependency, this description is very limited in its narrow focus, and fails to cover its many adverse effects. It is also extremely worrying, since increasing numbers of people are attending drug clinics for cannabis dependency. In the USA around 300,000 *new* individuals seek professional help for cannabis dependency each year (Herrmann et al, 2015). The United Nations Office on Drugs and Crime has published international consensus reports on its damaging health effects (UNODC, 2011, 2016), while the adverse psychiatric sequelae have also been reviewed (Volkow et al, 2014: Copeland et al, 2014). Herbal cannabis contains a number of different cannabinoids, including delta 9-THC which is psychoactive, and cannabidiol which is non-psychoactive (or minimally psychoative). Cannabidiol has been investigated for a range of potentially benefical medicinal properties (UNODC, 2016). It is however important that medicinal cannabidiol is used as a monosubsatnace (and not mixed with THC). The focus of this article is on herbal cannabis, which contains delta 9-THC and is being used for its psychoactive properties. One of our core aims is to explain how any acute mood gains, are ouweighed by its chronically damaging effects. The limited empirical data on artificial 'spice' cannabinoids will also be covered, noting that they can be even more damaging to human well-being (Zimmermann et al, 2009; Schifano et al, 2011, 2015; Downey et al, 2014; Gurney et al, 2014).

A second and rather more complex aim, is to compare the psychobiolgical effects of cannabis, with those of the recreational stimulants. The comparative effects of different CNS stimulant drugs, such as cocaine, nicotine, methamphetaime and MDMA, were the topic for an earlier review in this Human Psychopharmacology series (Parrott, 2015). The current article will debate the many psychobiological similarities between cannabis and the recreational stimulants. This undertaking may be perceived as a rather unusual, since sedative and stimulant drugs are

traditionally seen as quite different. There are, however, important precedents for debating them within the same theoretical framework. Wise and Bozarth (1987) noted that all addictive drugs displayed the 'common denominator' of activation of dopaminergic fibres, which led to similar patterns of compulsive drug self-administration. Koob (2009) focused on the role of allostatic load for all forms of drug dependency, with the dysregulation of hedonic-pleasure control, and impaired homeostasis. Hence all addictive drugs tended to heighten stress, with impairments both to the HPA axis, and to those neural regions underlying motivation and reward such as the amygdala. The current article takes a similarly broad and eclectic approach. It proposes that there are many similarities in the core psychobiological processses altered by these different drugs, and that they underlie the various forms of damage they cause in humans (Table 1).

Acute mood effects.

Cannabis is primarily a sedative drug, whereas CNS stimulant drugs are by definition activating and alerting. Hence acute cannabis typically leads to feelings of relaxation, whereas stimulant drugs increase physiological arousal and feelings of alertness. The neurotransmitter changes which underlie these alerting, sedative, and other psychopharmacological effects, are outlined in the follow reviews (Green et al, 2003; Cruickshank and Dyer, 2009; Hall, 2015; Panenka et al, 2013). Despite these fundamental differences in arousal between CNS stimulants and cannabis, there are a number of broad similarities in their overall mood effects. In particular the moods they engender comprise a mixture of positive or desired mood states, along with other less desirable mood state changes. For instance, the acute effects of recreational cannabis may include positive feelings of sociability, happiness, and calmness (Green et al, 2003; Titus et al, 2007); yet cannabis can also generate more negative feelings of anxiety, agitation, and suspiciousness (Volkow et al, 2014; Hall, 2015). Furthermore there are individual differences in these mood reactions, and they can influence the decision to continue (or discontinue) further drug usage. Le Strat et al (2009) investigated initial responses to cannabis, and found that those experimenters who reported 5 or more positive mood reactions were 28 times more likely to become regular cannabis users, than those who reported no positive mood reactions. One interesting research question is which factors cause this variability.

Adverse reactions typically occur more often after higher doses, although they also occur after low doses in some individuals. So do they reflect 'hard-wired' differences in personality and/or neurochemistry, or are they more related to psychological factors such as expectancy?

CNS stimulant drugs such as amphetamine and cocaine can also intensify a wide range of mood states, including some which are positive and desirable, and others which are more negative and undesirable. The positive effects of CNS activation can include feelings of sociability and happiness, while the more negative moods may include feelings of anxiety and tension (Cruickshank and Dyer, 2004; Parrott et al, 2004; Carvalho et al, 2013; Panenka et al, 2013). When higher doses are taken, the stimulatory effects can be far stronger, with recreational users reporting a physical *rush* or *hit*, along with feelings of elation or euphoria. Yet these higher doses can also lead to intensely negative moods, with pronounced feelings of tension, suspiciousness, or clinical paranoia (Carvalho et al, 2013; Panenka et al, 2013). These positive and negative mood effects can occur together, leading to changeable and unpredictable patterns of behaviour. Even the methamphetamine derivative MDMA, or 'ecstasy', traditionally seen as the most euphoriant of all the recreational stimulants, can paradoxically lead to feelings of anger and aggression (Reid et al, 2007). Indeed the mixture of positive and negative moods with MDMA, has been empirically shown to be similar to the mixed mood profiles generated by recreational cocaine (Parrott et al, 2011a), methamphetamine (Parrott et al, 2011b; Kirkpatrick et al, 2012), and mephedrone (Jones et al, 2016).

- Table 1 near here -

Drug withdrawal and repetitive mood vacillation

One of the core problems found with every psychoactive drug, is that the on-drug period is followed by a period of neurochemical rebound, when the opposite moods develop. All psychoactive drugs can cause these repetitive mood vacillations (Parrott, 2008). They may be illustrated by the legal stimulant nicotine, or by the illegal stimulant cocaine, since both drugs display rapid profiles of action. For a

detailed review of the many pharmacokinetic and pharmacodynamic similarities of nicotine and cocaine, in pre-clinical animal research, see Mello (2010). Physiologically nicotine is a powerful CNS stimulant, with the first cigarette of the day increasing resting heart rate by around 16 bpm, while 4mg nicotine gum can increase it by around 6 bpm (Parrott and Winder, 1989). Cigarette smokers report feeling more alert after their first cigarette of the day, but this activation is rapidly lost, with smokers soon *needing* another cigarette to maintain alertness. This craving for nicotine commences around 20-60 minutes after the last cigarette in regular smokers, illustrating how the essence of nicotine dependency is this repetitive vacillation in psychobiological states (see Figure 1 in Parrott, 1994). Similar patterns of mood fluctuation are also found with cocaine users. Nasal insufflation leads to a rapid hit, but this is soon followed by low moods, and the desire for another 'rush' or 'hit'. Hence cocaine, just like nicotine, displays a very high addiction potential (Cadet et al, 2007; Parrott, 2008, 2015; Mello, 2010; Carvalho et al, 2013).

Similar patterns of mood fluctuations are found with every other CNS stimulant. Cathinone has slightly weaker CNS stimulant properties than cocaine or amphetamine, and is self-administered by chewing Khat leaves. The drug-habit is common in countries around the Horn of Africa, and associated immigrant communities in Western cities (Parrott, 2007). The mood effects of cathinone have been summarised by Aden et al (2006). Khat chewers report mood gains when chewing, but these are soon followed by negative moods when not-chewing. The same pattern of positive moods on drug, followed by negative moods post-drug, is also evident with recreational MDMA or Ecstasy. This methamphetamine derivative displays a far longer time profile, so that the acute mood gains take 1 to 4 hours to develop and peak, and the post-MDMA recovery period may last for several days. Hence recreational Ecstasy/MDMA users report moods such as happiness or euphoria for a few hours (Parrott and Lasky, 1998), but they are followed by feelings of sadness and unsociability two days later. Curran et al (2004) also found very positive moods on-MDMA, but again they were followed by significant levels of aggression and depression in the days afterwards. This long pharmacodynamic profile helps to explain why Ecstasy/MDMA is typically used intermittently (Parrott, 2005).

A similar pattern of repetitive mood vacillation also occurs with cannabis. Vandrey et al (2005) compared the profiles of cannabis and tobacco withdrawal symptoms, and concluded that the 'magnitude and time course of withdrawal effects are similar across the two syndromes'. The unpleasant mood effects of cannabis withdrawal included irritability, anxiety, anger and depression; these negative feelings were commonly reported, although to a different extent across individuals (Budney et al, 2001; Vandrey et al, 2005; Allsop et al, 2014). These adverse feelings are commonly reported, with Vandrey et al (2005) finding that 2/3rds of their sample experienced 4 or more cannabis withdrawal symptoms. Other psychophysiolgial and behavioural effects of cannabis withdrawal can include psychmotor agitation, reduced appetite, and impaired sleep architecture. The breadth of these psychobiological symptoms can make cessation very difficult (Allsop et al, 2014). The key problem is that mood states on drug are followed by negative moods off-drug, so causing repetitive mood vacillations, and heightening the propensity for drug dependency. The above studies have typically employed standardised questionnaires, such as the Marijuana Craving Questionnaire (Heishman et al, 2001), and the Cannabis Withdrawal Discomfort Scale (Budney et al, 1999), to measure the severity of withdrawal symptoms.

Dependency and addiction potential.

It is widely recognised that all the recreational stimulants are addictive, and for an overview of the addictive properties of amphetamine, methamphetamine and cocaine, the following reviews are recommended (Cruickshank and Dyer, 2004; Carvalho et al, 2013; Panenka et al, 2013; Glasner-Edwards and Mooney, 2014). These reviews note that two of the most addictive stimulant drugs are 'ice' methamphetamine, and 'crack' cocaine, due to their strength and rapidity of action. Cannabis also shows strong addiction potential, with higher strength products such as 'skunk' being more addictive that normal herbal supplies (Copeland et al, 2014). The more recent artificial 'spice' cannabinoids, which an be *total* rather than *partial* agonists for the cannabinoid receptor, are even stronger in their addiction potential (Schifano et al, 2011, 2015; Steeley et al, 2012; Papanti et al, 2013; Downey et al, 2014). Indeed it

has been suggested that they can be just as addictive as the strongest CNS stimulants (Zimmermann et al, 2009).

In the USA, it has been estimated that around 300,000 individuals seek professional help for cannabis dependency each year (Herrmann et al, 2015). The proportion of cannabis users with clinical dependency has been estimated to be around 10% of those who have ever tried the drug (Wagner and Anthony, 2002). More recent reports suggest even higher rates of clinical problems, probably due to the more potent strains of modern cannabis (Copeland et al, 2014). Furthermore, a far higher proportion of cannabis users display sub-clinical levels of dependency. In one large survey of British users, 65% of recreational users reported some degree of cannabis dependence, although only 3% of this sample had sought clinical treatment (Terry et al, 2007). Regular cannabis users experience adverse moods during withdrawal, and the extent of these negative feelings predicts their 'difficulty in quitting' (Budney et al, 2004). Dependency is greater in frequent users, with around 50% of daily cannabis users showing clinical levels of dependency (Coffey et al, 2002). Young initiates are also more vulnerable, with commencement before age 17 years, demonstrating an *eighteen* fold increase in subsequent cannabis dependence (Silins et al, 2014). Dependent cannabis users suffer more from memory impairments, mental health problems, respiratory diseases, financial problems, conflicts with family/friends, and occupational or employment problems (Coffey et al, 2003).

The Hypothalamic-Pituitary-Adrenal Axis and homeostasis.

In physiological terms, good health and psychological stability are dependent on homeostasis. When homeostasis is disrupted, the organism displays psychological imbalance and increased levels of stress (Seyle, 1955). The Hypothalamic-Pituitary-Adrenal (HPA) axis underlies the maintenance of psychophysiological stability, with cortisol being the key neurohormone (Lovallo, 1997). Hence normal healthy individuals show a regular circadian rhythm of cortisol secretion, and when the HPA axis is disrupted, the organism typically shows signs of stress (Selye, 1955; Parrott, 2009). CNS stimulant drugs such as cocaine which activate the HPA axis, cause an increase in cortisol release, which leads to acute and/or chronic stress (Mello, 2010). Cortisol release is similarly heightened by MDMA. In the laboratory, Harris et al

(2002) found an acute cortisol increase of 150% after a moderate dose of MDMA. While in recreational Ecstasy/MDMA users, Parrott et al (2008) found an acute cortisol increase of 800%. Wetherell and Montgomery (2013) found that the Cortisol Awakening Response was altered in recreational Ecstasy/MDMA users. Cortisol can also be measured in 3-month hair samples, with regular Ecstasy/MDMA users displaying a 400% increase in this stress hormone (Parrott et al, 2014). Cannabis can also adversely affect the HPA axis. Raganathan et al (2009) showed that acute THC administration led to a significant increase in cortisol secretion. In large prospective study of Dutch adolescents, Van Leeuwen et al (2011) found that regular users of cannabis demonstrated lower hormonal reactivity to a standard laboratory test of social stress. King et al (2011) found that chronic cannabis users had significantly higher salivary cortisol levels than controls, and noted the implications for changes in psychomotor performance and brain activity.

Psychiatric aspects.

The world's oldest pharmacopeia, attributed to Emperor Shen Nung in China, noted that although cannabis had some useful medicinal properties: 'If taken in excess it will produce visions of devils' (Nung, 1998). Modern research has confirmed that cannabis can generate cognitive distortions and a range of psychiatric problems (Volkow et al., 2014). Acute cannabis can adversely affect cognitive integrity, by inducing bizarre thoughts and feelings of depersonalisation (Ashton, 2001). In a placebo-controlled laboratory study, D'Souza and colleagues (2004) administered THC to recreational cannabis users *without any prior psychiatric history*. Acute THC led to significant increases in schizophrenia-like symptoms, as assessed using the Positive and Negative Symptom Scale (PANSS). The emergent thoughts and bizarre cognitions included the following subjective experiences following acute cannabis: 'I thought I could see into the future …I thought I was god', another volunteer stated: 'I could hear someone typing on the computer…and I thought you were trying to program me'; while a third person noted: 'I thought you could read my mind, that is why I did not answer'; many other examples were also given (D'Souza et al, 2004). The extent of PANSS positive symptoms induced by tetra-hydrocannabinol has been shown to correlate with specific changes in brain activity (Nottage et al, 2015).

The psychotic-like effects of acute cannabis wear off as the drug is metabolised and excreted, but its regular use can lead to various forms of drug-induced psychosis, and other psychiatric problems (Paparelli et al, 2011). The Swedish Conscript study was the first prospective investigation to demonstrate an association between cannabis and schizophrenia (Andréasson et al, 1987). It has been followed by several further prospective studies, and they have also found that recreational cannabis leads to an increased risk of psychotic breakdown in later years. In a comprehensive review, Le Bec et al (2009) concluded that every prospective study showed a link between cannabis use, and the later emergence of psychosis or psychotic symptoms. One important modulating factor is the premorbid personality, since some individuals are more susceptible to psychiatric breakdown. Henquet et al (2005) prospectively followed 2437 young cannabis users with or without a predisposition for psychosis, and found an increased risk in both groups, although the effect was more pronounced in the predisposed group (Henquet et al, 2005). As with many studies, a highly significant dosage effect was present. Cannabis users who used the substance 'less than monthly' showed no increase in psychotic symptoms (OR= 0.99), those who took it '1-2 times/week' showed a significantly increased risk (OR=1.95), and this was further increased in those who used cannabis 'almost daily' (OR=2.23). Cannabis use was also associated with other chronic mental health problems, including depression, anxiety, and mania (Richardson, 2010; Bovasso, 2014; Patton et al., 2002; Van Laar et al, 2007). Again dosage effects are typically noted, with heavier users showing the greater risk. Lubman et al (2015) noted that the 'endocannabinoid system plays an important part in brain development', and suggested that this may explain why heavy cannabis use during adolescence was associated with 'more severe and persistent negative outcomes', including cognitive impairment and mental illness. Levine et al (2017) similarly noted the strong association between heavy cannabis use during adolescence, and adverse psychiatric/cognitive outcomes, but noted that it was still unclear whether 'cannabis alone' was the causal factor. They further noted that the animal literature showed that 'adolescent-onset exposure to cannabinoids can catalyze molecular processes that lead to persistent functional deficits in adulthood', and recommended future longitudinal studies with carefully integrated batteries of assessment measures.

The recreational use of CNS stimulants is also associated with greater psychiatric distress. Even comparatively weak CNS stimulants such as cathinone, can lead to psychiatric problems. Feyissa and Kelly (2008) undertook a functional review of Khat chewing, and concluded that cathinone could induce a range of 'mood disturbances, particularly depression' in otherwise normal subjects, while some regular users developed a form of hypomania. The authors further noted that many of the problems of cathinone users were similar to those occurring in regular amphetamine users. Indeed the chronic use of recreational amphetamine, cocaine, and methamphetamine, can lead to a wide range of adverse psychobiological and/or psychiatric consequences (Cadet et al, 2007; Cruickshank and Dyer, 2009; Panenka et al, 2013). The adverse psychophysiolgical effects may include tremors, dyskinesias, repetitive stereotypical movements, while the adverse psychiatric effects can include anxious irritability, anger or physical aggression, feelings of paranoia, and full psychosis (Williamson et al, 1997; Fasano et al, 2008; Cruickshank and Dyer, 2009; Panenka et al, 2013; Vearrier et al, 2012; Glaser-Edwards and Mooney, 2014). MDMA is a methamphetamine derivative, and despite being called 'Ecstasy', is also associated with a range of adverse psychiatric consequences (Schifano et al, 1998; MacInnes et al, 2001; Parrott et al, 2001, 2014a,b; Scholey et al, 2011). Brière et al (2012) undertook a prospective study of disadvantaged Canadian schoolchildren, and found that youngsters who commenced taking recreational MDMA reported significantly higher depression one year later [Note: a similar pattern of increasing depression was also found with novice methamphetamine users]. While in another prospective study, Turner et al (2014) found that females who quit taking Ecstasy/MDMA, reported significantly lower levels of depression over a year later. In contrast, in a large cross-sectional study, Taurah et al (2013) found that former users continued to display high levels of depression, along with other psychobiological deficits such as impulsiveness, poor memory, and disturbed sleep.

Neurocognitive effects.

Many cognitive skills are impaired by acute cannabis, including memory, learning new information, sustained attention, higher cognitive abilities such as decision making, and more basic abilities such as psychomotor integrity. The regular use of cannabis can also lead to a range of cognitive deficits in abstinent users, with the

extent of these deficits related to factors, such as frequency and duration of recreational usage (Pope et al, 2001; Bolla et al, 2002; Grant et al, 2003; Yücel et al, 2008). The adolescent brain may also be more susceptible to the adverse effects of cannabis (Jager et al, 2010). In long term users who ocmm durin adolescence, there may even be a slow decline in intelligence test scores over time (Meier et al, 2012). Neuroimaging studies show that two brain regions particularly affected by cannabis are the hippocampus and amygdala, since although cannabinoid receptors are found across the whole brain, these regions display high levels of cannabinoid receptor density. Dose-related reductions in hippocampal and amygdala volumes have also been reported (Yucel et al, 2008). In a review of the adverse effects of cannabis on brain structure and activity, Mandelbaum and de la Monte (2016) noted that: 'Neuroimaging studies demonstrated that the major targets of cannabis-mediated neurodegeneration include white matter in the frontal lobes, fornix, fimbria of the hippocampus, frontal-limbic connections, corpus callosum, and commissural fibers. In addition, cannabis targets the cerebellar structure and function such that cerebellar white matter atrophy can be significant and associated with neurobehavioral deficits and psychotic symptoms'.

The recreational use of cocaine, methamphetamine and MDMA, are also associated with neurocognitive impairments. Cruickshank and Dyer (2009) noted that methamphetamine use was associated with impairments in executive functioning, learning of new information, various aspects of memory, and impairments in motor skills. The similarity of this list to that described for cannabis users in the previous paragraph, may be noted. Many other reviews have generated similar lists of neurocognitive impairments, following the use of other CNS stimulant drugs. Cocaine users display a wide range of neuropsychological and neurocognitive deficits (Soar et al, 2012), with deficits in attention, memory, and executive functioning (Vonmoos et al, 2013). Drug-free Ecstasy/MDMA users demonstrate deficits in retrospective memory with a meta-analysis showing moderate-to-large effect sizes (Laws and Kokkalis, 2007). Other neurocognitive deficits are found with prospective memory, executive planning, and problem solving, while complex visual processing can also be affected (Fisk et al, 2005; Fox et al, 2002; Mejias et al, 2005; Montgomery et al, 2010).

Summary and overview.

There are several ways for CNS stimulant drugs to damage the neuropsychobiological integrity of the organism. In overall terms, they disrupt psychological equilibrium, by acutely stimulating multiple mood states, then impairing them during the post-drug recovery period. This vacillation in mood states may be seen as an index for more profound psychological changes. So that feelings of alertness, confidence, motivation, and sociability, can all show similar patterns of repetitive vacillation. Psychobiological vacillation also raises questions over their efficacy and safety, when stimulant drugs such as MDMA are being used for medicinal or therapeutic purposes (Parrott, 2014). It also explains why every CNS stimulant displays a strong addiction potential. The regular user suffers from many negative states when off-drug, and feels correspondingly better when on-drug; this underlies their desire to take the drug repeatedly (Parrott, 1994, 2008). All stimulant drugs adversely affect the HPA axis, causing hormonal dysregulation, and increasing the susceptibility for psychiatric distress (Table 1). In an earlier review (Parrott, 2015) it was noted that the healthy human organism displays a natural balance between sympathetic and parasympathetic nervous system activity. When humans used recreational stimulant drugs, they disturbed this natural balance, and this led to numerous adverse consequences (Parrott, 2015).

Cannabis induces a similar pattern of disrupted homeostasis, despite being primarily a sedative. It causes moods to fluctuate, and as with the recreational stimulants, this provides the core rationale for its addiction potential (Table 1). The regular user may feel 'better' on-drug, but afterwards they develop feelings of anxiety, anger, or other negative mood states when off-drug. Again this repetitive mood fluctuation helps to explain cannabis's strong addiction potential. Cannabis also affects the HPA axis, and by impairing homeostasis, it can disrupt psychological integrity and impair sleep (Table 1). The cognitive skills which are impaired by cannabis, are also broadly similar to those damaged by recreational stimulants such as cocaine or amphetamine. Cannabis can also leads to a wide range of psychiatric problems, with spice cannabinoids showing an even greater propensity for psychobiological/psychiatric abreactions (Fergusson et al, 2003; Zimmermann et al, 2009; Nottage et al, 2015). In summary, despite their very

different effects on arousal and feelings of alertness, cannabis and the recreational stimulants display a surprisingly similar profile of acute and chronic psychobiological effects.

Finally, it is important to educate society about the adverse effects of all these psychoactive drugs. Proponents for drug use typically focus on acute drug effects, and with this narrow focus, any psychoactive drug could be misperceived as beneficial (Parrott, 2008). It is only by covering all aspects of their acute and chronic usage that a total picture of their damaging effects emerges. Governments need to fund basic education campaigns, describing their adverse health and psychobiological consequences. Public health campaigns have been effective at educating the public about the adverse effects of tobacco smoking, and have led to massive reductions in tobacco usage, while similar or are needed for excessive drinking (Parrott et al, 2016). Similar education campaigns are urgently needed for both herbal cannabis, and the artificial spice cannabinoids.

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Table 1. Core psychobiological processes underlying the effects of recreational cannabis and CNS stimulant drugs.

	Summary of main effects		
Positive/desired acute mood effects	Range of positive mood changes found with both classes of drug. Positive moods tend to be activating/alerting with CNS stimulants, and sedative/relaxant with cannabis (.	Cruickshank and Dyer, 200? Le Strat et al, 2009 Hall, 2015	
Negative/unwanted acute mood effects	Range of negative mood changes reported with both types of drug. Feeling of stress, tension, and loss of control.	Carvalho et al, 2013 Volkov et al, 2014	
Post drug withdrawal	Negative moods such as irritability and depression tend to predominate, with similar patterns of drug withdrawal following CNS stimulants such as nicotine, and sedatives such as cannabis.	Parrott and Lasky, 1998 Parrott 1999 Vandree et al, 2005	
Repetitive mood fluctuations, as indices of broader changes psychological state	All psychoactive drugs by definition cause moods to fluctuate. These mood state changes provide a surface index for wider and more fundamental fluctuations in psychological status. They also provide the psychobiological basis for drug addiction.	Aden et al, 2006	
Addiction potential	This reflects two core factors: strength, and rapidity of action. Addiction potential is greater in stronger drugs. Hence spice cannabinoids are more addictive than plant-derived street cannabis. Addictiveness greater in drugs with a rapid onset and withdrawal, such as 'crack' cocaine.	Budney et al, 1999 Copeland et al, 2014 Herrmann et al, 2014	
Impaired homeostasis	Changes to the Hypothalamic Pituitary Adrenal (HPA) axis, with altered patterns of cortisol release, and many other neurohormonal Homeostasis adversely affected, with altered patterns of sleep and waking, often accompanied by increased stress.	Van Leeuwen et al, 2011 Parrott et al, 2014a,b	
Psychiatric deficits	Recreational stimulants associated with many forms of psychiatric distress. Acute cannabis can elicit strange thoughts and cognitions. Chronic cannabis use may lead to psychosis and other psychiatric disorders.	Volkov et al, 2014 Downey et al, 2014 Schifano et al, 2011 Brier et al, 2013	
Neurocognitive deficits and neuroimaging measures brain activity	Neuroimaging and neurocognitive studies reveal a range of deficits. Deficits in working memory, attention, declarative memory, and higher cognitive skills, found in regular users of cannabis and CNS stimulants. Neuroimaging studies reveal chronic changes in brain activity.	Yucel et al, 2008 Kish et al, 2010 Taurah et al, 2013 Mandelbarum et al, 2016	