The acute and non-acute effects of cannabis on reward processing: A systematic review

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Abstract

Cannabis use has historically been thought to cause amotivation, but the relationship between cannabis and apathy, anhedonia, and reward processing remains poorly characterised. In this systematic review, we evaluated whether cannabis exposure acutely and/or non-acutely was associated with altered reward processing using questionnaire, behavioural, or functional neuroimaging measures. Questionnaire studies demonstrated greater anhedonia in adolescent cannabis users, and some indication of greater apathy in young adult cannabis users. Behavioural studies yielded some evidence of reduced reward learning in adolescent cannabis users, though there were too few studies in this category for reliable conclusions. Finally, longitudinal and acute functional neuroimaging studies showed an association between cannabis and blunted neural responses to reward, which did not emerge consistently in cross-sectional studies. The current results suggest that cannabis use is associated with specific impairments in reward and motivation. Future large-scale, longitudinal studies which use multiple behavioural and neuroimaging measures of reward processing may further clarify the impact of cannabis use on motivational and reward processes, and neural networks.

Keywords: Cannabis use, THC, reward processing, anhedonia, apathy, motivation, MID task

1. Introduction

Cannabis is one of the most commonly used psychoactive substances worldwide, among both adults and adolescents (UNODC, 2020). Cannabis has historically been thought to cause amotivation (McGlothlin & West, 1968), but the idea that cannabis users are lazy and apathetic is predominantly informed by cultural tropes rather than scientific evidence. Recently, researchers have broadened their focus to investigate whether cannabis users generally respond to or evaluate rewards differently from controls, but a comprehensive synthesis of findings is currently missing.

"Reward processing" is a multi-faceted concept which refers to any neural, psychological, or behavioural process that underpins the seeking and consumption of rewards (Berridge, Robinson, & Aldridge, 2009). Reward processing deficits can take the form of apathy or anhedonia, whereby apathy refers to a loss of or reduction in motivation, and anhedonia to a loss of interest in or pleasure from previously rewarding activities (Robert et al., 2009; Treadway & Zald, 2011). Although apathy is sometimes equated with motivation, it is best understood as reduced interest in seeking rewards specifically, rather than motivation generally (which is a more inclusive term). Previously, researchers have characterised reward processing without a coherent framework of subdomains. However, Husain and Roiser (2018) suggest that the umbrella term of "reward processing", as well as hedonic/motivational deficit syndromes such as apathy and anhedonia, might be better understood through examining the specific sub-processes involved. An influential framework proposed by Berridge et al. (2009) conceptualises reward processing as consisting of three phases including an appetitive phase (reward "wanting", or incentive salience), a consummatory phase (reward "liking", or hedonic impact), and a learning phase. To the authors' knowledge, there has been no review to date synthesising findings on cannabis and reward processing across different sub-processes and

methodologies. This is important, as results are likely to differ depending on which sub-process is assessed.

Δ^9-tetrahydrocannabinol (THC), the main psychoactive compound in cannabis, acts on the brain's endocannabinoid (ECB) system as a partial agonist of CB_1 receptors (CB_1Rs). CB_1Rs are densely populated in prefrontal and limbic areas involved in reward and motivation (Glass, Dragunow, & Faull, 1997), where they regulate dopaminergic, γ-aminobutyric acid (GABA)ergic, and glutamatergic signalling. The ECB system plays an important role in facilitating reward processing in the brain, through modulation of dopaminergic and opioidergic neurotransmission (Parsons & Hurd, 2015; Solinas, Goldberg, & Piomelli, 2008; Wang & Lupica, 2014; Wenzel & Cheer, 2018). Reward processing impairments feature frequently in theories of substance use disorders (SUDs; e.g. Berridge & Robinson, 2016; Blum et al., 2000; Goldstein & Volkow, 2002), and altered reward processing has been found for various substances of abuse (e.g. Balodis & Potenza, 2015). Cannabis use has been associated with greater impulsivity (Clark, Roiser, Robbins, & Sahakian, 2009), and a systematic review by Pacheco-Colón, Limia, and Gonzalez (2018) found some evidence for a causal link between cannabis use and reduced motivation. Adolescents may be particularly vulnerable to the harmful effects of cannabis, including disrupted reward processing, due to the important frontal and limbic neuromaturation occurring during this time (Bossong & Niesink, 2010; Giedd, 2004; Giedd et al., 1999; Lubman, Cheetham, & Yücel, 2015; Schneider, 2008). Indeed, in another review, Pacheco-Colón, Ramirez, and Gonzalez (2019) found that adolescent cannabis use was strongly associated with academic outcomes and depression, but there was insufficient evidence to conclude whether cannabis use negatively impacted motivation in this age group.

In the current systematic review, we address the association between cannabis use and reward processing. We focus on both acute studies involving assessment after cannabis

intoxication, and non-acute studies involving assessment of cannabis users in a non-intoxicated state. We aimed to address the following questions:

1) Is cannabis use associated with greater levels of anhedonia and apathy as indicated by questionnaire measures?
2) Is cannabis use associated with altered performance on behavioural tasks of reward processing non-acutely?
3) Is cannabis use associated with altered neural correlates of reward processing non-acutely?
4) What are the acute effects of cannabis on reward processing outcomes?

As a secondary aim, we also investigated potential differences between adult and adolescent age-groups on the above outcomes. We performed a systematic review of the extant literature on cannabis use and reward processing in humans, which quantified reward function using questionnaires, behavioural tasks, or functional neuroimaging. To our knowledge, this is the first comprehensive review of reward processing in cannabis use including both non-acute and acute studies, and a broad spectrum of outcomes.

2. Methods

The current systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015). It was registered on PROSPERO in April 2020, prior to data extraction (PROSPERO ID: CRD42020180000).

2.1 Inclusion/exclusion criteria

Inclusion criteria for all studies were publication of original data in a peer reviewed journal, and assessment of apathy, anhedonia, or a reward sub-process with a questionnaire, behavioural, or neuroimaging measure. Task and measure inclusion for behavioural and functional neuroimaging studies was guided by the Berridge et al. (2009) framework of anticipatory/motivational responses, consummatory/hedonic responses, and reward learning. Only human studies of natural/non-drug rewards were considered eligible. Non-acute studies were included if they: 1) compared a cannabis user group with a non-using control group, 2) compared a light/occasional user group with a heavy user group, or 3) correlated levels of use with outcome measures in either a longitudinal or cross-sectional design. Acute studies had to be placebo-controlled, single- or double-blinded, and randomised. Study samples were defined as adolescent if mean age at assessment was less than 18 years, and adult if mean age at assessment was greater than or equal to 18 years.

Studies were excluded if participants were recruited on the basis of: 1) primarily using a drug other than cannabis (alcohol and/or tobacco use was permissible), 2) having a history of substance abuse/dependence (other than cannabis, for the users), 3) having a history of psychiatric disorder (other than cannabis abuse/dependence), and/or 4) having a mean age of ≥ 65 years. We did not include studies of simple neurobiological differences without assessment with a cognitive task. We also did not include studies of punishment/avoidance behaviour, attentional bias, responses to affective pictures, gambling and decision-making tasks, or inter-temporal choice tasks. As these tasks tap into other processes (e.g. impulsivity, loss aversion), we did not consider them as consistent with the Berridge et al. (2009) framework. Reasons for exclusion are reported in Figure 1.

2.2 Search strategy and data extraction

A search was made in Medline, Embase, and PsycInfo on 10/01/2020, with additional studies identified through PubMed publication alerts. The search was performed by MS, and results were stored using Rayyan (Ouzzani, Hammady, Fedorowicz, & Elmagarmid, 2016). Table S1 contains the exact terms and strategy used to search each database. MS and CL performed title/abstract and full-text screening separately, and discrepancies were resolved through discussion. Figure 1 describes the study selection process.

Data extraction was performed by MS, and checked by CL. Bias assessment was performed independently by MS and CL, using the Quality Assessment Tool for Quantitative Studies as a guide (Effective Public Health Practice Project, 1998; see Figure S1). Following preliminary discussions, there were initial disagreements on global ratings for two studies.

We also performed simple power calculations for questionnaire and behavioural studies using the 'pwr' package in R 3.6.2 (Champely, 2020; R Core Team, 2019). Power calculations were based on *t*-tests or correlations, depending on study design. Small, medium, and large effects were estimated as Cohen's *d* values of 0.2, 0.5, and 0.8, respectively, or correlations *r* of .1, .3, and .5, respectively. The cut-off for desired power was set to 80%.

3. Results

The final sample comprised 30 papers including 31 studies, of which 26 were non-acute (Tables 1a and 1b) and five were acute (Tables 2a and 2b). Two (Freeman et al., 2018; Lawn et al., 2016) had participants from the same sample, but as they used different tasks, we included both. Total number of participants were 5546 in the questionnaire studies, 401 in the non-acute behavioural studies, 712 in the non-acute neuroimaging studies, and 48 in the acute

studies. All included studies obtained informed consent from participants. Task explanations are provided in Box 1. For studies that assessed responses to reward outcomes, "hedonic impact" will be used to refer to responses measured while a reward (e.g. food or music) was consumed/enjoyed, while "reward feedback" will be used to refer to tasks where the participants were informed that they had been successful in obtaining a reward (e.g. money), but did not receive it immediately.

3.1 Questionnaire studies

Ten questionnaire studies were identified by our search. Four studies measured apathy, all using the Apathy Evaluation Scale (AES). Of these, two (Meier & White, 2018; Petrucci, LaFrance, & Cuttler, 2020) suggested greater levels in young adult cannabis users, while the other two found no differences between cannabis users and controls using adult (Barnwell, Earleywine, & Wilcox, 2006) and adolescent (Pacheco-Colón, Coxe, et al., 2018) samples. Petrucci et al. had the largest sample by a margin (n = 1168). While any lifetime cannabis use was associated with lower levels of apathy in this study (r = -.100), apathy correlated positively with quantity of cannabis use (r = .118), scores on the Cannabis Use Disorder Identification Test (CUDIT, r = .107), and scores on the Marijuana Problems Scale (MPS, r = .125), after controlling for depression, alcohol and other substance use, and personality traits. There was no significant association between apathy and frequency of use or age of onset, neither before or after covariate control. Conversely, Barnwell et al. (2006) found no group differences in apathy using another large sample of 243 daily users and 244 controls.

Six studies measured anhedonia, using the Snaith-Hamilton Pleasure Scale (SHAPS), Social and Physical Anhedonia Scales (SAS and PAS), and the Temporary Experience of Pleasure Scale (TEPS). Of the four studies including adult samples, three (Cassidy, Lepage,

Harvey, & Malla, 2012; Dumas et al., 2002; Ford et al., 2014) found no significant relationship between cannabis use and anhedonia. However, Lopez-Vergara, Jackson, Meshesha, and Metrik (2019) found a positive association between cannabis use and anhedonia using the SHAPS, in adult users with minimum weekly use. Two studies used adolescent samples. Dorard, Berthoz, Phan, Corcos, and Bungener (2008) found higher scores on the SAS and PAS in adolescent cannabis users, compared to controls. Leventhal et al. (2017) employed a longitudinal design, with participants aged 14 at baseline, and included the largest sample of any study assessed (n = 3394). In this study, baseline levels of anhedonia predicted future cannabis use, while the reverse association was not significant. There was also a cross-sectional association between cannabis use and anhedonia at baseline.

3.2 Behavioural studies

For the present purposes, a behavioural task encompasses all non-neuroimaging and non-questionnaire outcomes. Studies that fit this description are reported together, even though they assessed different reward processes. There were a total of four non-acute studies which assessed a behavioural reward processing outcome.

Two studies measured willingness to expend effort for reward, roughly corresponding to reward "wanting" in the Berridge et al. (2009) framework; Lane, Cherek, Pietras, and Steinberg (2005) using a progressive ratio task in an adolescent sample, and Lawn et al. (2016) using the Effort Expenditure for Reward task in an adult sample. While Lane et al. found evidence of reduced motivation in cannabis users, Lawn et al found no significant differences between the user group and control group. In the latter study, participants also performed the Probabilistic Reward task, which measures reward learning as a function of response bias towards more frequently rewarded stimuli. Results revealed poorer reward learning in users

relative to controls, but this effect was fully attenuated when controlling for depressive symptoms and cigarette use. This paper also included an acute study, which is reported in section 3.4. Finally, Castellanos-Ryan et al. (2017) measured reward learning using a card playing task, in a longitudinal study of 294 males from low socioeconomic status (SES) backgrounds. They found that cannabis use at age 14 predicted declined reward learning from age 13 to age 20.

Two studies investigated subjective responses to rewards, corresponding to reward "liking" in the Berridge et al. (2009) framework. Both used adult age groups. Martin-Soelch et al. (2009) found reduced mood responses to positive feedback/reward in cannabis users for easy trials of a spatial delayed response task. Zimmermann et al. (2019) examined pleasantness ratings to social reward (male and female closeness and touch) in abstinent dependent cannabis users and controls. There were no overall group differences in pleasantness ratings, though an exploratory analysis revealed a lower increase in ratings from the male to the female examiner in the cannabis group relative to the control group. These were behavioural results from a functional magnetic resonance imaging (fMRI) paradigm (see section 3.3).

3.3 Functional neuroimaging studies

There were 13 non-acute neuroimaging studies, all using fMRI. Most employed the Monetary Incentive Delay (MID) task (Knutson et al., 2000). Common versions of the MID task include neutral, reward/win, and loss trials, but we will not report results for loss trials as negative incentive processes are not the focus of this review. The anticipation phase of the MID task can be considered as corresponding to reward "wanting" and the feedback phase as corresponding to reward "liking" in the Berridge et al. (2009) framework.

Firstly, we will consider studies of reward anticipation in adults and adolescents. There were seven studies measuring neural activity during reward anticipation in adults. Using whole-brain analyses, two studies found no differences between adult cannabis users and controls during MID reward anticipation (Enzi et al., 2015; Yip et al., 2014). Conversely, Nestor, Hester, and Garavan (2010) found higher activity in the right striatum and cerebellum, and van Hell et al. (2010) found lower activity in several prefrontal and striatal regions, in cannabis users relative to controls. Three studies performed region of interest analyses in the ventral striatum or nucleus accumbens (NAc), of which one (Yip et al., 2014) found no difference between cannabis users and controls, and two (Martz et al., 2016; van Hell et al., 2010) revealed lower anticipatory activity in users. Martz et al. (2016) employed a longitudinal design with participants aged 18-24 years at baseline, and found that cannabis use was prospectively associated with blunted anticipatory NAc activity at two- and four-year follow-ups. Finally, Lichenstein, Musselman, Shaw, Sitnick, and Forbes (2017) investigated functional connectivity between NAc and prefrontal/anterior cingulate cortex (PFC/ACC) to win vs. loss trials of a card guessing task, and found no differences between adults with stable high or escalating cannabis use during adolescence, and a stable low use control group. There were three studies of adolescent users, all using the MID task. Two found no differences between cannabis users and controls in regional anticipatory activity using a whole-brain analysis (Jager, Block, Luijten, & Ramsey, 2013) and a region-of-interest analysis in the NAc (Karoly et al., 2015). In contrast, Nestor, Behan, Suckling, and Garavan (2020) found greater global network integration and frontolimbic functional connectivity in adolescent users compared to controls.

Secondly, we will consider studies of reward feedback. There were six studies including adult users. These gave evidence of both higher (van Hell et al., 2010) and lower (Nestor et al., 2010; van Hell et al., 2010; Yip et al., 2014) activity in cannabis users across several brain

regions, including prefrontal, limbic, and sensorimotor sites. However, other studies found no differences between users and controls (Filbey, Dunlop, & Myers, 2013), including those performing region of interest analyses in the ventral striatum (van Hell et al., 2010; Yip et al., 2014). Lichenstein et al. (2017) found lower and negative connectivity between the NAc and medial PFC in the escalators group compared to the stable low group, the latter showing positive connectivity. Moreover, negative connectivity between the NAc and the medial prefrontal region differentiating groups at baseline, predicted higher anhedonia at a two-year follow-up assessment. Two studies assessed reward feedback in adolescent samples. Acheson et al. (2015) found higher reward feedback activity in the middle frontal gyrus and caudate in adolescent cannabis users compared to controls, using a coin toss task. The two groups showed no differences in effective connectivity. Finally, Jager et al. (2013), found no differences between adolescent cannabis users and controls during MID reward feedback.

Two studies measured brain activity to hedonic impact, both in adult age groups. Ford et al. (2014) found no differences between cannabis users and controls during music listening, though cannabis use was positively correlated with activity in the medial frontal cortex in a third group with major depressive disorder. Zimmermann et al. (2019) found decreased activity in the right putamen during the touch/presence of a female examiner in male cannabis users, in contrast to increased activity in the same region in male controls, relative to baseline.

3.4 Acute studies

Our search identified five studies investigating the effects of acute cannabis on a reward processing outcome, all of which used adult samples. Apart from Jansma et al. (2013), no acute study controlled for cigarette/nicotine use. There were two behavioural studies, both including THC and cannabidiol (CBD) conditions. In the acute experiment reported in Lawn et al. (2016)

cannabis without CBD led to a reduction in the likelihood of making a high-effort choice on the Effort Expenditure for Reward task relative to placebo. Additionally, results showed increased sensitivity to reward magnitude changes at low probability of reward for cannabis without CBD compared to cannabis with CBD. This study also examined the acute effects of cannabis on state-level anhedonia, and found no differences between active cannabis and placebo. de Bruijn, de Graaf, Witkamp, and Jager (2017) investigated the effect of acute THC, CBD (without THC), and placebo on the reported liking and sweetness intensity of chocolate milk, and found no differences between the three conditions.

Three studies assessed the effect of acute cannabis on neural responses to rewards with fMRI. Using the MID task, Jansma et al. (2013) found reduced anticipatory activity in the NAc after acute THC administration in a group of nicotine dependent participants, which was not present for non-nicotine dependent participants. van Hell et al. (2012) found higher activity in the right orbitofrontal cortex during reward anticipation, and lower activity in the right superior frontal gyrus during reward feedback, during active cannabis relative to placebo. However, follow-up analyses within individual regions of interest did not reach statistical significance after correcting for multiple comparisons. Finally, Freeman et al. (2018) found that THC dampened the response to music in several brain areas associated with music listening and pleasure, including auditory cortex and ventral striatum. Moreover, functional connectivity between these two areas was higher during a THC with CBD condition, compared to a THC only condition. Notably, THC (with or without CBD) did not alter subjective enjoyment of music in this study.

4. Discussion

In the current systematic review, we aimed to evaluate the impact of cannabis use on reward processing. This is the first comprehensive review on this topic, including both acute and non-acute studies, and a broad spectrum of reward processing outcomes. Figure 2 shows a conceptual diagram of the non-acute studies, and their results.

4.1 The association between cannabis use, apathy, and anhedonia

Collectively, the reviewed studies yielded equivocal evidence for an association between cannabis use and apathy. Petrucci et al. (2020) and Barnwell et al. (2006) had the largest samples (1168 participants and 487 participants, respectively), thus their findings should be weighted more heavily. Although these studies yielded conflicting results, Barnwell et al. (2006) did not include all questionnaire items of the AES, and had higher risk of bias than Petrucci et al. (2020) (see Figure S1). In particular, Barnwell et al. did not assess or control for mental health variables or other drug use. Additionally, participants in the Barnwell et al. study had a higher mean age (33.1 years) than in Petrucci et al. (20.5 years). The other study to include young adults (19.9 years) also found higher levels of apathy in cannabis users compared to controls (Meier & White, 2018).

The observed correlations between apathy and various indices of problematic cannabis use corresponded to small effects (r = .11-.13) after controlling for covariates (Petrucci et al., 2020). Petrucci et al. was the only study powered to detect a small effect, whereas Barnwell et al. was the only additional study powered to detect a medium effect (see Table 1a). Thus, although we can probably exclude a large association between cannabis use and apathy based on the current literature, there may be a small association with problematic cannabis use in

young adult users. Future investigations are needed to determine whether this finding replicates in adolescent cannabis users as well.

The majority of studies in adult users did not find an association between cannabis use and anhedonia. Conversely, both studies using adolescent samples (i.e. Dorard et al., 2008; Leventhal et al., 2017) found a significant association between cannabis use and anhedonia, suggesting that age could be an important factor. Both studies were estimated to have low risk of bias. Leventhal et al. (2017) was the only longitudinal study in the sample, and included the largest number of participants (n = 3394) of any study reviewed. They also controlled for important factors, including mental health disorders and polysubstance use. In this study, baseline levels of anhedonia predicted future cannabis use, but baseline levels of cannabis use did not predict future anhedonia. This suggests that anhedonia is a predisposing factor towards cannabis use during adolescence, though whether anhedonia causes or merely precedes cannabis use is unclear.

Importantly, studies reporting significant associations between cannabis use and anhedonia tended to find small-to-medium effects. In addition to differences in sample age, the three studies that did not find a significant relationship had lower power overall compared to the three that did. They also did not have sufficient power to detect small effects. This supports the conclusion that cannabis use may be related to anhedonia during adolescence. Individual studies do not point to such an association in adulthood, although the possibility of a small effect cannot be excluded based on the current literature.

4.2 The association between cannabis use and behavioural assessments reward processing

Cannabis users are commonly thought of as lacking motivation, and the reviewed literature did suggest a putative association between cannabis use and questionnaire measures

of apathy in young adults. However, there were only two studies assessing motivation using laboratory tasks, as indicated by willingness to expend effort for reward. While Lane et al. (2005) found evidence of lower motivation in adolescent users, Lawn et al. (2016) found no differences between adult users and controls. This difference could be attributable to greater vulnerability in adolescents to a motivational impairment of cannabis. However, the two studies also used different tasks, and level of cannabis use among the control participants was higher in Lawn et al. than in Lane et al. Thus, heterogeneity in cannabis use, including among control participants, could also partly explain the difference in results. Importantly, motivation is a multi-faceted concept, and is also linked to general self-efficacy, reward and punishment sensitivity, and achievement approach, all of which may be related to cannabis use (Petrucci et al., 2020). Thus, the association between cannabis and motivation is likely complex, and more studies, using a variety of measures, are needed to establish whether cannabis use does in fact cause amotivation.

Reward learning is a core component of several models of reward processing (e.g. Husain & Roiser, 2018; Zald & Treadway, 2017), however, there were only two studies which examined the relationship between reward learning and cannabis use. Lawn et al. (2016) found that differences in reward learning between adult cannabis users and controls dissipated when controlling for depressive symptoms and tobacco use. In contrast, Castellanos-Ryan et al. (2017) found that cannabis use in early adolescence was predictive of reduced reward learning into early adulthood among low SES males, also controlling for tobacco and other drug use. This study also had lower risk of bias and higher power than the Lawn et al. study. Their results thus support an association between adolescent cannabis use and impairments in reward learning, although findings should be replicated and extended to include use of alternative tasks, as well as females and participants with higher SES.

Finally, there was tentative evidence of reduced hedonic capacity in adult cannabis users compared to controls, as revealed by Martin-Soelch et al. (2009) and Zimmermann et al. (2019). However, both studies had low power, and in both studies a significant relationship was only found for certain task trials and/or statistical tests. Further research is therefore needed to corroborate these results, before a conclusion can be made. Future studies should also consider utilising non-ambiguous rewards that allow for clear in-the-moment assessments of pleasure, such as food or music.

4.3 The association between cannabis use and fMRI measures of reward processing

The reviewed evidence suggests that cannabis users recruit the same networks as controls during reward processing, similar to other cognitive processes (Bloomfield et al., 2019). However, there were a number of differences in regional activity and functional connectivity during reward anticipation, reward feedback, and hedonic impact.

Cross-sectional studies of reward anticipation yielded mixed results, with some finding increased activity or connectivity among cannabis users, others finding decreased activity, and some finding no significant differences between cannabis users and controls. Similarly, there was comparable evidence indicating attenuation and enhancement of neural responses to reward feedback in cannabis users. There were no clear differences in results according to age groups. Discrepant findings also did not appear to be attributable to amount/frequency of use, length of abstinence, or relevant confounders, though there was a tendency towards slightly higher risk of bias in studies finding no significant differences. Martz et al. (2016) was an important key study, as it was the only longitudinal investigation to include a large number of participants of both sexes and control for relevant confounders. In this study, past-year cannabis use predicted attenuated NAc activity during monetary reward anticipation at future timepoints.

The NAc is consistently implicated in reward (Liu, Hairston, Schrier, & Fan, 2011) and addiction processes (Robbins & Everitt, 2002), and attenuated ventral striatal responses to rewarding stimuli might be indicative of anhedonia (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005; Wacker, Dillon, & Pizzagalli, 2009). Interestingly, Martz et al. (2016) found no cross-sectional association between reward anticipation at baseline and previous cannabis use. This suggests that pre-existing differences in reward networks between groups may obscure this relationship in cross-sectional studies. Thus, it may be that cannabis use predicts attenuated reward anticipation activity in the NAc over time, but not cross-sectionally.

The two studies measuring some aspect of reward consumption suggested minor blunted neural responses to social reward in cannabis users (Zimmermann et al., 2019), but no differences for music reward (Ford et al., 2014). Studies of reward feedback showed a tendency towards hyperactivity in dorsal striatal and prefrontal areas in cannabis users (Acheson et al., 2015; Enzi et al., 2015; van Hell et al., 2010). Thus, cannabis users may overactivate parts of the brain's reward network during reward feedback. Importantly, this finding was not replicated by all studies (Filbey et al., 2013; Jager et al., 2013; Nestor et al., 2010; Yip et al., 2014). Discrepant results did not appear to be attributable to age, amount/frequency of use, or length of abstinence. However, the three studies finding frontostriatal hyperactivity in cannabis users did not report any method of control for other drug use, whereas the four other studies had at least some control of this covariate. Thus, we cannot rule out the possibility that concurrent tobacco, alcohol, or other illicit drug use contributed to this finding. Furthermore, given that the MID task is better suited to measure reward anticipation than reward feedback, future studies should replicate this finding using alternative tasks.

4.4 Acute effects of cannabis on reward processing

The results of Lawn et al. (2016) suggested an acute amotivational effect of cannabis at low probability of reward, consistent with previous research (Cherek et al., 2002). However, acute cannabis did not affect liking of food (de Bruijn et al., 2017) or pleasure ratings of music (Freeman et al., 2018). This was surprising, given the vast amount of historical, anecdotal, and preclinical scientific evidence suggesting that that cannabis augments the pleasurable effects of a variety of rewards (see Solinas et al., 2008 for a review). THC has for instance been shown to increase hedonic reactions to sweet tastes and decrease aversive reactions to bitter tastes in animals (Jarrett, Limebeer, & Parker, 2005; Jarrett, Scantlebury, & Parker, 2007). It may be that the lack of food and music choice, and the unnatural setting in which food consumption and music listening took place (e.g. inside an MRI scanner in Freeman et al.) blunted the effect of THC on subjective enjoyment in these studies. Additionally, THC may have a stronger anticipatory as opposed to consummatory effect during reward processing. Cannabis famously causes "the munchies" in humans (Roberts, Jager, Christiansen, & Kirkham, 2019), and in Freeman et al., ratings for 'want to listen to music' increased after THC exposure, suggesting that acute cannabis increases the desirability of both food and music. Thus, it could be that THC potentiates anticipation and enjoyment of self-selected and desired rewards in natural settings, but not pre-selected rewards in laboratory settings.

Previous research has shown that THC both increases and decreases activity and functional connectivity in specific brain regions during performance of different cognitive tasks (Bloomfield et al., 2019). Interestingly, Jansma and colleagues found reduced anticipatory activity in the NAc after THC administration in nicotine dependent participants, but THC had no consistent effects on reward anticipation in participants without nicotine dependence (Jansma et al., 2013; van Hell et al., 2012). Freeman et al. (2018) found attenuated neural responses to music listening in areas associated with reward. These results were consistent with

those of van Hell et al. (2012), who found a general blunting effect of THC during reward feedback on both successful and unsuccessful trials of the MID task. Thus, although acute cannabis did not affect self-rated enjoyment of rewards in the reviewed studies, THC appears to attenuate neural responses during reward feedback and hedonic impact. Future research should attempt to tease apart the relative impact of acute cannabis on neural responses and subjective pleasure during anticipation and consumption of reward.

4.5 Caveats and suggestions for future research

Several important caveats may account for the variability in findings discussed in the present review. Firstly, studies varied considerably in how reward processing (the dependent variable) and cannabis exposure (the independent variable) were operationalised. Cannabis exposure was not consistently quantified, and ranged from recreational to heavy/problematic use in user groups, and from no use to recreational use in control groups. Additionally, age of onset, duration of use, and duration of abstinence varied greatly, and were often not reported. The large span in time since last use is notable, given potentially divergent effects during residual intoxication, withdrawal, and abstinence (e.g. Schreiner & Dunn, 2012). However, given the current sample size, it was difficult to assess the impact of these and other important factors on the results. This methodological heterogeneity thus constitutes a problem for comparing studies within the same category of investigation.

Secondly, a significant proportion of the studies reviewed had only partial or no control for important confounders which might intersect with cannabis use to produce unique impairments to reward processing outcomes, such as polysubstance use (e.g. Balodis & Potenza, 2015; Hatzigiakoumis, Martinotti, Giannantonio, & Janiri, 2011; Luijten, Schellekens, Kühn, Machielse, & Sescousse, 2017) and depression (e.g. Eshel & Roiser, 2010).

The potential interaction with nicotine use is especially important. Karoly et al. (2015) found blunted reward anticipation responses in the NAc in a group of adolescent tobacco users, but not in a comparison group of adolescent cannabis users, without concurrent tobacco use. Additionally, Jansma et al. (2013) found significant effects of acute THC only in participants with nicotine dependence. These results suggest that it is important to report nicotine use in studies that examine effects of acute and long-term cannabis use. Less than half of the studies included in the present sample controlled for cigarette/tobacco use, and there were no clear differences in results between studies that did and did not include this covariate.

Future research should attempt to clearly quantify and report cannabis exposure in user and control groups (e.g. see proposal of a standard THC unit by Freeman and Lorenzetti (2020)), and any sub-analyses should be decided a priori. Polysubstance use and mental health disorders must be evaluated, and particular care should be devoted to disentangling putative effects of cannabis and nicotine. Future studies should also include more female and adolescent cannabis users. Substance use is usually initiated in adolescence, a time when cannabis use may be uniquely influential in disrupting normal brain development, potentially resulting in adverse outcomes such as abnormal cognitive development and psychopathology (Bossong & Niesink, 2010; Lubman et al., 2015; Schneider, 2008). For instance, there is ample evidence that adolescents are more vulnerable to cannabis use disorder (Chen, O'Brien, & Anthony, 2005; Chen, Storr, & Anthony, 2009; Ehlers et al., 2010) and to the addictive aspects of acute cannabis (Mokrysz, Freeman, Korkki, Griffiths, & Curran, 2016) compared to adults. In spite of this, none of the acute studies and only a third of the non-acute studies included adolescent cannabis users. Female cannabis users were also underrepresented in the literature, particularly in neuroimaging studies. Several studies have found divergent associations between cannabis and neurocognitive functioning according to sex, potentially attributable to activational effects of gonadal hormones and sexual dimorphism in the endocannabinoid system (Craft, Marusich,

& Wiley, 2013; Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Crane, Schuster, Mermelstein, & Gonzalez, 2015). Future studies should therefore also take care to include female cannabis users.

4.6 Conclusions

A systematic review of the literature on cannabis use and reward processing suggests that anhedonia is associated with cannabis use during adolescence. There was little evidence of a relationship between anhedonia and cannabis use in adulthood, although low power may have precluded studies from detecting a significant effect. Additionally, there was tentative evidence for a weak association between problematic cannabis use and apathy in young adults. Behavioural studies showed reduced reward learning in adolescent cannabis users, although there were too few studies in this category for reliable conclusions. One relatively large longitudinal fMRI study found that cannabis use predicted blunted neural responses during reward anticipation, though smaller cross-sectional fMRI studies did not demonstrate a clear relationship between cannabis use and reward processing. Finally, studies investigating the effects of acute cannabis revealed blunted neural activity during reward feedback and hedonic impact after THC administration.

Importantly, the nature of the association between cannabis use and reward processing impairments is unclear. Some individuals could be predisposed towards cannabis use in an attempt to counteract a hyporesponsive reward system (e.g. Blum et al., 2000), or a third variable (e.g. depression) could be the primary cause of both. Conversely, cannabis may have a neurotoxic effect, disrupting the brain's ability to process reward cues and outcomes (Rocchetti et al., 2013). Repeated THC exposure can result in downregulation of CB_1R expression globally and in the ventral striatum (Ceccarini et al., 2015; Hirvonen et al., 2012),

which may impair the sensitivity of the ECB system to rewarding stimuli in cannabis users (see e.g. Bloomfield, Morgan, Kapur, Curran, & Howes, 2014), and increase their susceptibility to anhedonia (Volkow, Hampson, & Baler, 2017).

The reviewed research had significant methodological heterogeneity, and questionnaire and behavioural studies were generally low-powered. Future research should include a greater proportion of adolescent and female cannabis users, and attempt to clearly quantify cannabis exposure in user and control groups, define and target specific reward sub-processes, and assess and control for nicotine and polysubstance use, and comorbid mental health conditions. Understanding the association between cannabis use and reward processing impairments is important to development of novel treatments for cannabis use disorder, informing policy-makers, and recognising the mechanisms by which cannabis use may contribute to the onset of various mental health conditions.

Acknowledgements

None.

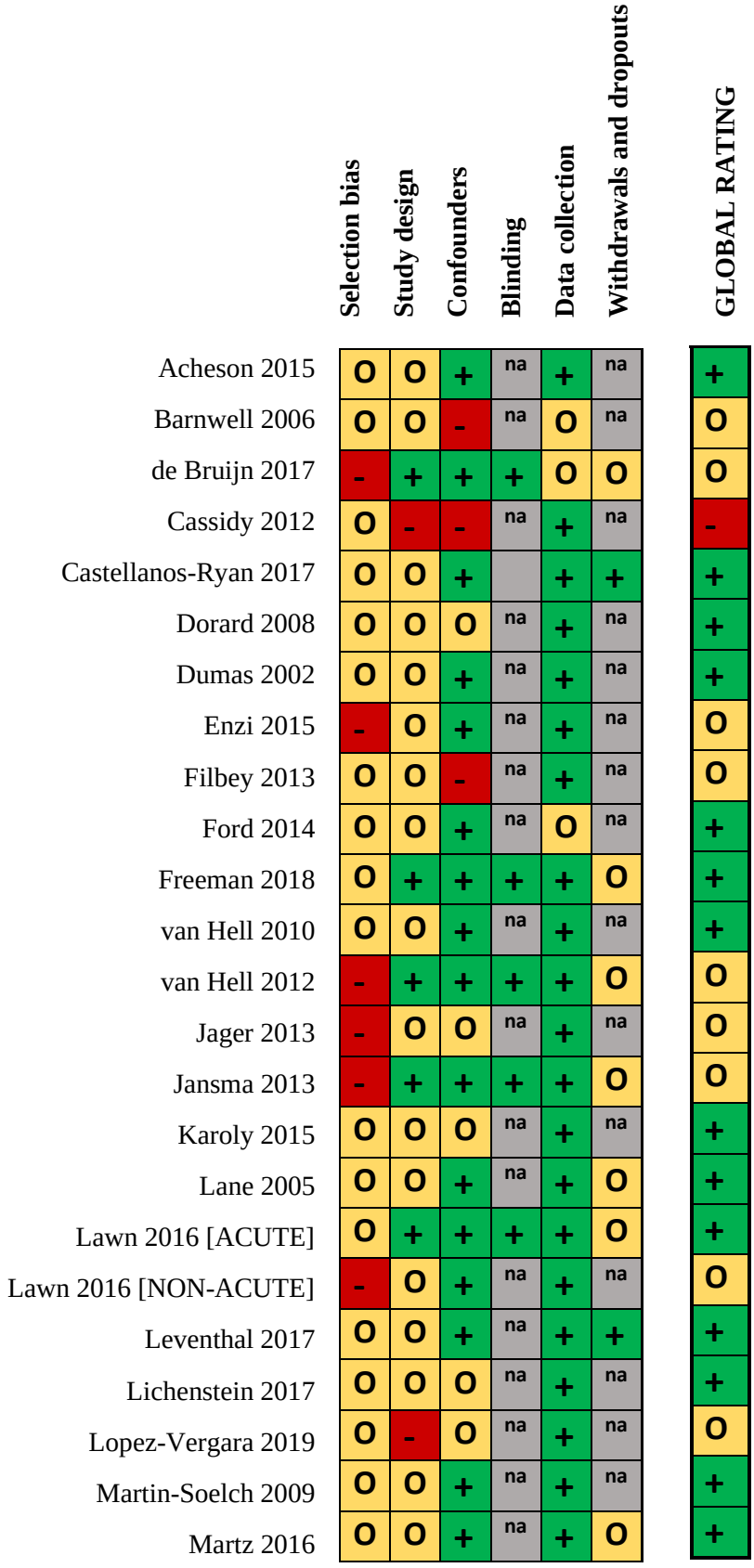
Appendix

Table S1. Search terms

	Medline & Embase: Cannabis terms
	Cannabi*.ab,ti. Cannabis/ THC*.ab,ti. Tetrahydrocannabi*.ab,ti. Marijuana*.ab,ti. Marijuana Abuse/ exp “Marijuana Use”/
	Medline & Embase: Reward processing terms
	Reward*.ab,ti. Reward/ Reinforce*.ab,ti. Incentive*.ab,ti. Motivat*.ab,ti. Motivation/ “Nucleus accumbens”.ab,ti. Anhedoni*.ab,ti.
	Medline & Embase: Animal terms
	Monkey*.ti. Rat*.ti. Rodent*.ti. Mouse*.ti. Mice*.ti. Animal*.ti.
	PsycInfo: Cannabis terms
	Cannabi*.ab,ti. (DE "Cannabis" OR DE "Hashish" OR DE "Marijuana") THC*.ab,ti. Tetrahydrocannabi*.ab,ti. DE «Tetrahydrocannabinol» Marijuana*.ab,ti. DE “Cannabis Use Disorder” DE "Marijuana Usage"
	PsycInfo: Reward processing terms
	Reward*.ab,ti. (DE "Rewards" OR DE "External Rewards" OR DE "Internal Rewards" OR DE "Monetary Rewards" OR DE "Preferred Rewards") Reinforce*.ab,ti. Incentive*.ab,ti. Motivat*.ab,ti. DE «Motivation» “Nucleus accumbens”.ab,ti. Anhedoni*.ab,ti.
	PsycInfo: Animal terms

	Monkey*.ti. Rat*.ti. Rodent*.ti. Mouse*.ti. Mice*.ti. Animal*.ti.

Note. Cannabis terms and reward processing terms were combined within categories with "OR" and between categories with "AND". Animal terms (search performed in the title only) were combined with the resulting search pool using "NOT", in order to quickly filter out irrelevant studies.


Selection bias
Study design
Confounders
Blinding
Data collection
Withdrawals and dropouts
GLOBAL RATING
Acheson 2015 O O + na + na +
Barnwell 2006 O O - na O na O
de Bruijn 2017 - + + + O O O
Cassidy 2012 O - - na + na -
Castellanos-Ryan 2017 O O + + + +
Dorard 2008 O O O na + na +
Dumas 2002 O O + na + na +
Enzi 2015 - O + na + na O
Filbey 2013 O O - na + na O
Ford 2014 O O + na O na +
Freeman 2018 O + + + + O +
van Hell 2010 O O + na + na +
van Hell 2012 - + + + + O O
Jager 2013 - O O na + na O
Jansma 2013 - + + + + O O
Karoly 2015 O O O na + na +
Lane 2005 O O + na + O +
Lawn 2016 [ACUTE] O + + + + O +
Lawn 2016 [NON-ACUTE] - O + na + na O
Leventhal 2017 O O + na + + +
Lichenstein 2017 O O O na + na +
Lopez-Vergara 2019 O - O na + na O
Martin-Soelch 2009 O O + na + na +
Martz 2016 O O + na + O +

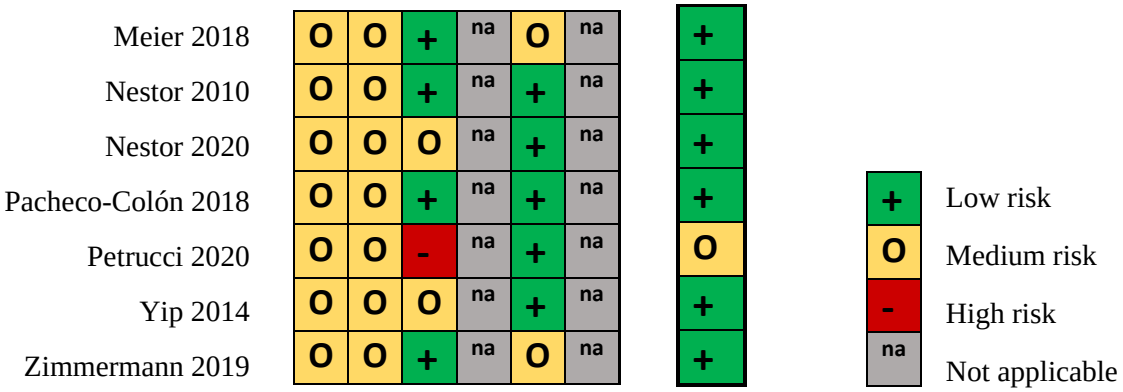


Figure S1. Bias assessment.

Note. Bias assessment was performed using the Quality Assessment Tool for Quantitative Studies (EPHPP, 1998). According to these criteria: studies with two or more high-risk component ratings receive a high-risk global rating; studies with one high-risk component rating receive a medium-risk global rating; and studies with no high-risk component ratings receive a low-risk global rating. Studies received a high-risk-rating for selection bias if they had not sufficiently described the recruitment procedures. The majority of studies received a medium-risk-rating for selection bias because they did not describe the rate of participation (percentage of individuals contacted that agreed to participate), but also if they had recruited only university students or males.

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Figures and tables

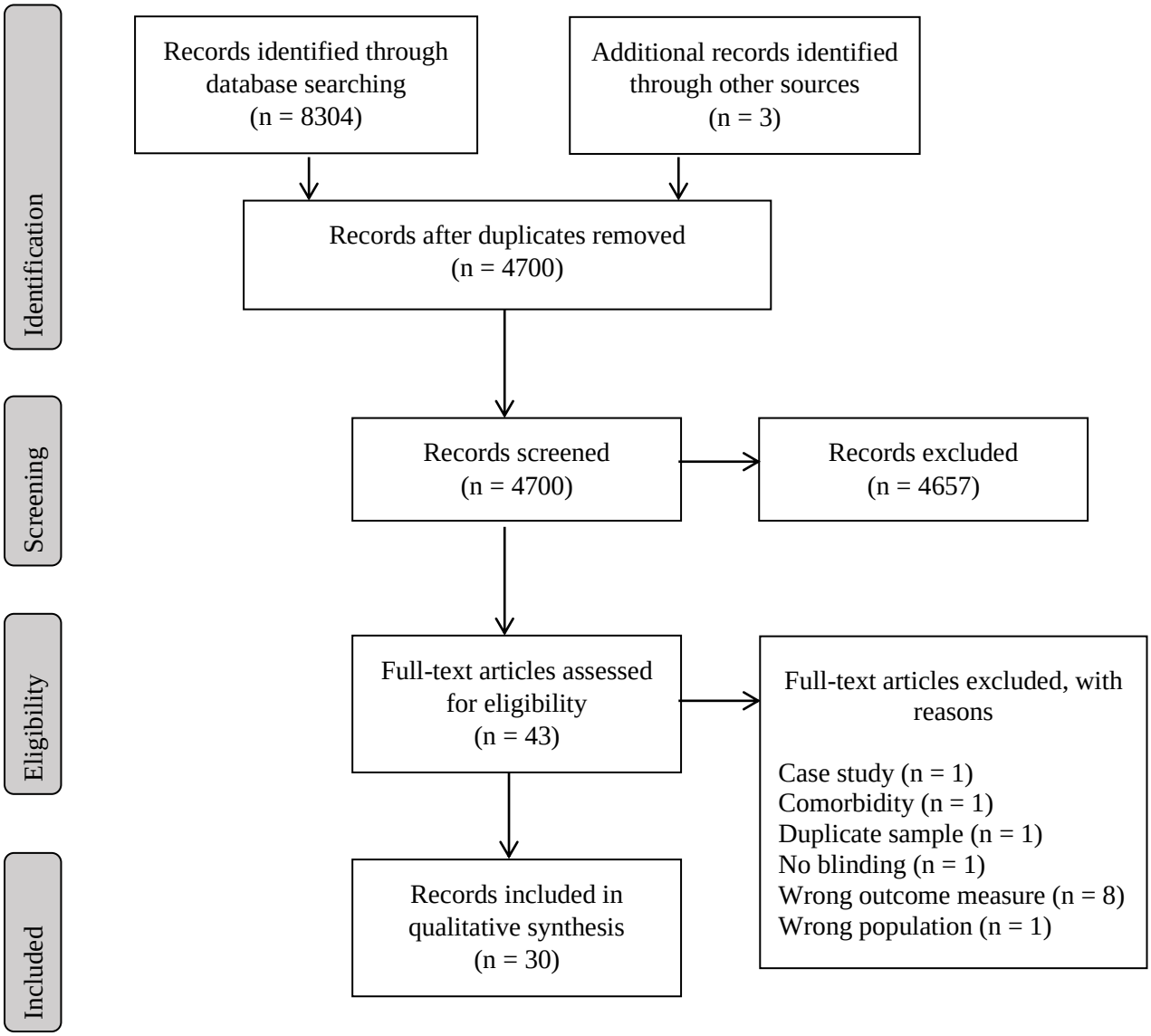

Figure 1. Study selection process

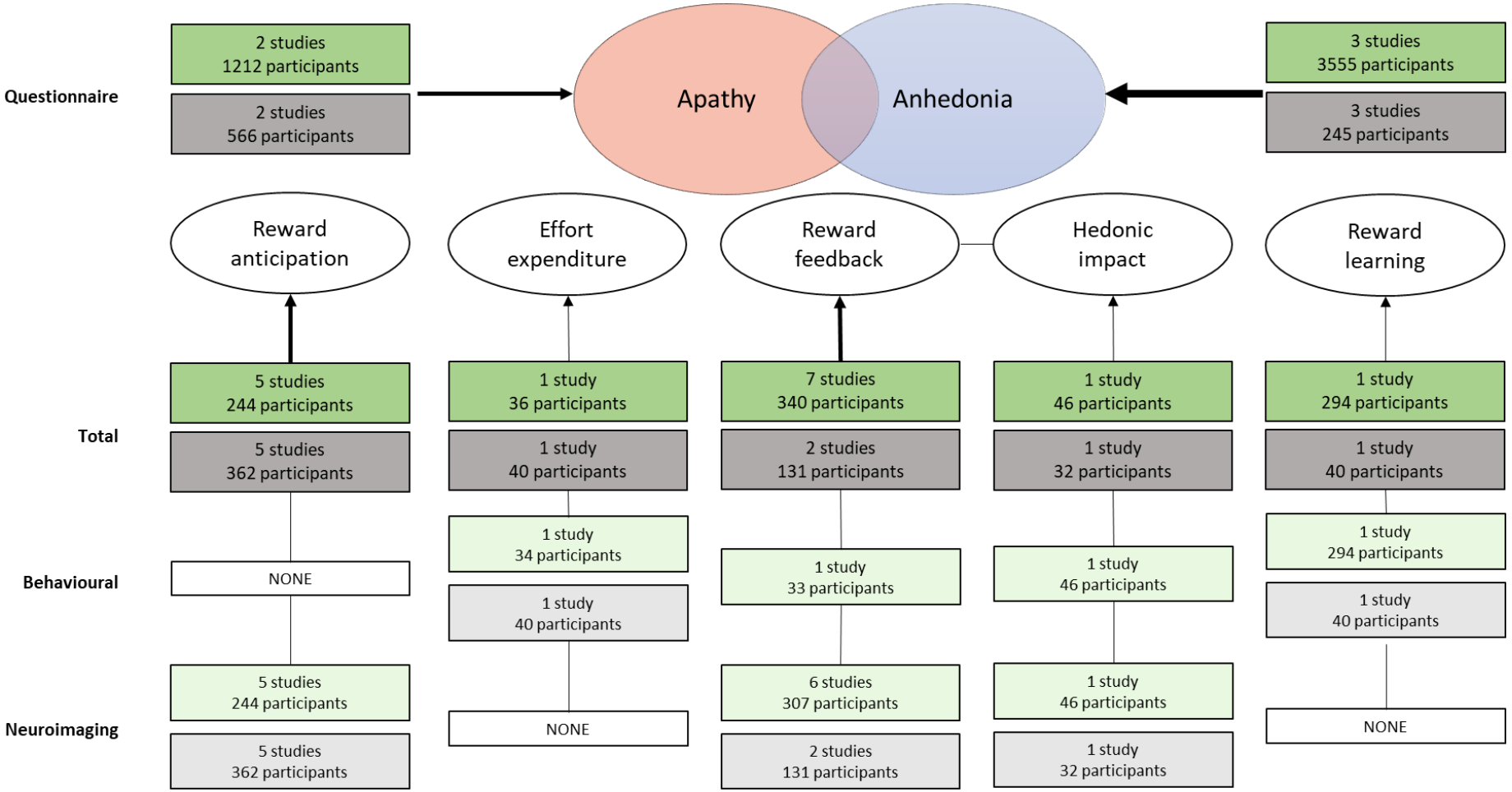

Figure 2. Conceptual diagram of the non-acute studies. Green colour indicates significant differences between cannabis users and controls, and grey colour indicates no significant differences. Thickness of arrows indicates the strength of the association, based on the number of studies, reported effects, and statistical power of studies in each category.

Table 1a. Behavioural/questionnaire studies

Author (year)	**Users/ Controls** n (females)	**Age** Mean age in years users/ controls, group	**Use frequency** Mean, unless otherwise stated	**Age of onset** Mean, unless otherwise stated	**Duration of abstinence**	**Controlled cigarette/ tobacco use?**	**Measure**	**Reward type**	**Results**	**Smallest detectable effect size at 80% power**	**Comments**
Questionnaire											
Barnwell et al. (2006)	243(46)/ 244(120)	33.1*, adult	7 days/week	NR	NR	No	AES	-	ns	Medium	
Cassidy et al. (2012)	46(-)	24.3*, adult	≥ 1 days/ month	NR	NR	No	TEPS anticipatory		ns	Large	Main comparison was between psychosis patients and healthy controls. Results reported here are for correlations with frequency of cannabis use in actively using controls (minimum 1 day/month of use).
							TEPS consummatory	-	ns		
Dorard et al. (2008)	27(5)/ 30(11)	17.2/16.7, adolescent	≤ 2 days/week (n = 4) to daily (n = 19)	13.3 (first use)	NR	No	SAS		Users > controls	Large	There was also a positive correlation with use quantity, for both scales.
							PAS	-	Users > controls		
Dumas et al. (2002)	41(6)/ 126(81)	21.1/21.3, adult	≥ 2 days/week	NR	NR	No	SAS	-	ns	Medium (at 79% power)	Includes an occasional user group, which did not score significantly different from the other two groups.
							PAS		ns		
Leventhal et al. (2017)	3394 (1816)	14.1**, adolescent	Any past 6 months (n = 76) to ≥ 15 days/ month (n = 73)**	≤ 14 years (n = 475) (unknown amount)	NR	Yes	SHAPS	-	Baseline SHAPS negatively predicted future cannabis use Baseline cannabis use	Small	Longitudinal study with follow-up assessments at 6, 12, and 18 months. The association of baseline anhedonia with future cannabis use was amplified for adolescents with peer cannabis use, but there was

									did not predict future SHAPS		no moderating effect of gender or baseline ever use.
Lopez-Vergara et al. (2019)	104(38)	29.3, adult	21.4 days/ month	NR	≥ 15 hours	Excluded if smoking > 20 cigarettes/ day	SHAPS	-	Negative association with cannabis use ns for cannabis problems	Medium	Structural equation modelling between factors of dysregulation, including a combined predictive factor of SHAPS and TPQ scores, and outcome factors cannabis problems and cannabis use. There were also significant bivariate correlations between SHAPS and cannabis use frequency, but not between SHAPS and cannabis problems, abuse, or dependence. All participants were users, with minimum weekly use.
Meier & White (2018)	17(6)/ 27(20)	19.9/19.3, adult	≥ 1 days/week	NR	NR	Yes	AES	-	Users > controls	<80% power to detect a large effect	AES scores were informant-reported.
Pacheco-Colón et al. (2018)	36(13)/ 43(24)	16.2/16.2, adolescent	≥ 10 days/ month	13.25 (unknown amount)	NR	Yes	AES MES	- -	ns ns	Large	Controls were light cannabis users.
Petrucci et al. (2020)	874(-)/ 294(-)	20.5*, adult	8.95 days/ month	16.6 (first use)	NR	No	AES	-	Negative correlation with user status Positive correlation with quantity, CUDIT, and MPS	Small	For the correlation with user status, controls were coded 0 and users were coded 1. When not controlling for covariates, the correlation with user status became non-significant. Results for additional measures of motivation not reported here.

									ns for frequency and age of onset		
Behavioural											
Castellanos-Ryan et al. (2017)	294(0)	13**, adolescent	Any past 12 months (n = 8) to ≥ 40 times past 12 months (n = 4)**	From 14 (n = 27), 15 (n = 46), 16 (n = 32), & 17 (n = 21)	NR	Yes	CAPT	Money	Cannabis use at 14 years predicted a decline in performance from 13 to 20 years	Medium	Longitudinal study with annual follow-up assessments until 17 years, and again at 20 years. CAPT performance at 13 years was not a significant predictor of cannabis use at 14 years, change in use between 14 and 17 years, or age of onset. Change in cannabis use between 14 and 17 years and age of onset did not predict change in CAPT scores from 13 years to 20 years.
Lane et al. (2005)	14(4)/ 20(7)	16.8/16.2, adolescent	≥ 4 days/week	NR	≥ since evening before	Excluded	PRT	Money	Users < controls	<80% power to detect a large effect	Lower effort indicated by earlier switch to FT option (lower PRT completed), and greater % of earnings derived from FT option.
Lawn et al. (2016) [non-acute]	20(7)/ 20(6)	27.8/27.3, adult	28.19 days/ month	NR	≥ 12 hours	Yes	EEfRT Probabilistic reward task	Money	ns Users < controls	<80% power to detect a large effect	Response bias used to indicate reward learning. All effects were fully attenuated when adjusted for scores on the Beck Depression Inventory and cigarette use.
Martin-Soelch et al. (2009)	14(6)/ 19(9)	24.6/25.2, adult	5.8 joints/ week	NR	≥ since evening before	Groups were matched	Mood rating task	Money	Users < controls for easy difficulty/low reward level	<80% power to detect a large effect	Includes an additional group of cigarette smokers, results not reported here.

* Reported for the combined sample.

**Values at baseline (longitudinal study)

Note. For the SHAPS, higher scores indicate greater ability to experience pleasure. Power calculations were based on *t*-tests or correlations, depending on study design. Cut-offs for small, medium, and large effects were set to Cohen's *d* values of 0.2, 0.5, and 0.8, respectively, or correlations *r* of .1, .3, and .5, respectively.

Abbreviations.

Tests & tasks: AES – Apathy Evaluation Scale, CAPT – card-playing task, CUDIT – Cannabis Use Identification Test, EEfRT – Effort Expenditure for Reward Task, MES – Motivation and Engagement Scale, MPS – Marijuana Problems Scale, PAS – Physical Anhedonia Scale, PRT – Progressive Ratio Task, SAS – Social Anhedonia Scale, SHAPS – Snaith-Hamilton Pleasure Scale, TEPS – Temporal Experience of Pleasure Scale, TPQ – tridimensional personality questionnaire

Other: DPW/M/Q/Y – days per week/month/three months/year, FT – fixed time, JPW/M/Y – joints per week/month/year, NA – not applicable, NR – not reported, ns – not significant

Table 1b. fMRI studies

Author (year)	**Users/ Controls** n (females)	**Age** Mean age in years users/ controls, group	**Use frequency** Mean, unless otherwise stated	**Age of onset** Mean, unless otherwise stated	**Duration of abstinence** Mean, unless otherwise stated	**Controlled cigarette/ tobacco use?**	**Measure**	**Analysis method**	**Reward type**	**Results**	**Comments**
Acheson et al. (2015)	14(3)/ 14(3)	17.6/17.3, adolescent	6.7 days/week	NR	≥ since evening before	No	Coin toss task reward feedback	ROI for regions with task-effects across groups Effective connectivity with unified SEM in results-based ROIs	Money	ROI: ↑ MFG, caudate, claustrum SEM: ns	
Enzi et al. (2015)	13(0)/ 13(0)	26.3/27.1, adult	13.87 joints/ week	15.87 (unknown amount)	1.1 days	No	MID reward anticipation reward feedback	WB + follow-up with ROI	Money	Anticipation: ns Feedback: Controls, but not users, differentiated between gain and neutral trials in L caudate and L IFG Users had greater activity in the L caudate and L IFG during the neutral	There was a positive correlation between lifetime joints and reward feedback activity in L caudate, but correlations of brain activity with blood THC levels, age of onset, cannabis use, and abstinence were not significant.

										feedback condition.	
Filbey et al. (2013)	59(13)/ 27(22)	23.5/30.3, adult	82.52 days/ quarter	15.04 (first use)	≥ 72 hours	No	MID reward anticipation reward feedback	WB	Money	ns	Results are reported for reward anticipation > neutral anticipation. For reward anticipation > loss anticipation, cannabis users had greater activity in precuneus, L MFG, and L postCG at a lower statistical threshold. Anticipation activity in OFC and ACC correlated negatively with withdrawal, at a lower statistical threshold. No correlations with SCID of abuse/dependence. Please see full paper for additional subgroup analyses according to alcohol consumption and level of dependence.
Ford et al. (2014)	15(5)/ 17(11)	20.2/20.0, adult	22 days/ month	≤ 17 (n = 8) (unknown amount)	NR	No	Music listening SHAPS	WB	Music	ns	Additional groups of MDD patients with and without concurrent cannabis use. Cannabis use was positively correlated with activity in the medial frontal cortex in the MDD+cannabis group.

											There was less than 80% power to detect a large effect for the SHAPS.
Jager et al. (2013)	21(0)/ 24(0)	17.2/16.8, adolescent	741 joints/year	13.2 (unknown amount)	5.1 weeks	No	MID reward anticipation reward feedback	WB + ROI in R & L caudate, and R & L putamen	Money	Anticipation: ↑ L caudate, R caudate (trend), R putamen (trend) during neutral trials Feedback: ns	Significant negative correlation between R caudate response during neutral anticipation and age of onset. Correlations for other ROIs, lifetime use, and past year use were not significant.
Karoly et al. (2015)	14(3)/ 38(14)	15.8/15.8, adolescent	20.4 days/ month	m = 12.93 (first use)	≥ 3 hours	Groups were matched	MID reward anticipation	ROI in R & L NAc	Money	ns	Additional cannabis+ polysubstance (with concurrent tobacco, or alcohol and tobacco use), tobacco only, and alcohol only groups. Significant differences only between tobacco group and remaining groups.
Lichenstein et al. (2017)	47(0)/ 111(0)	20.1/20.1, adult	17.5 days/ month	13.31/ 15.47 (first significant use, stable/ escalating users)	NR	Yes	Card guessing task reward anticipation reward feedback	PPI between NAc and PFC/ACC	Money	ns Escalating users < controls	Anticipation and feedback contrasts for win > loss. Users were split into a stable high (n = 11) and escalating (n = 36) group, controls were light users. Escalating users had negative connectivity, stable high and stable low users had positive connectivity during reward feedback. Regressions indicated no association with

											age of onset and recent use. Negative connectivity during feedback predicted greater anhedonia at age 22.
Martz et al. (2016)	108(39)	20.1**, adult	17.5 days/ year**	NR	48 hours	Yes	MID reward anticipation	ROI in NAc	Money	↓ NAc	Longitudinal study, with follow-up assessments at 2 and 4 years. Past-year use was negatively associated with NAc activity at 2 and 4 years. The correlation between baseline NAc activity and previous use was not significant, but there was a marginally significant negative correlation for age of onset.
Nestor et al. (2010)	14(2)/ 14(3)	22.1/23.1, adult	20.1 days/ month	16.1 (unknown amount)	108 hours	Groups were matched	MID reward anticipation reward feedback	Anticipation: ROI for regions with task-effects across groups Feedback: WB	Money	Anticipation: ↓ L FFG ↑ R striatum, R CB Feedback: ↓ PCL	Post hoc tests with a higher threshold suggested that the R striatum result was driven by putamen. Positive correlation between (a) years of use and (b) lifetime joints with anticipation activity in R medial frontal gyrus, L cingulate (lifetime joints only), R cuneus, R VS, R putamen, and R CB.

											Negative correlation between withdrawal and anticipation activity in FFG. There were significant differences during neutral feedback, which are not reported here.
Nestor et al. (2020)	18(1)/ 18(1)	16.5/16.1, adolescent	177.22 joints/ month	12.88 (unknown amount)	≥ since evening before	No	MID reward anticipation	Global connectivity strength with graph theory measures ROI-to-ROI functional connectivity	Money	Global connectivity: Users > controls Functional connectivity: Users > controls in a subnetwork comprising amygdala, NAc, HC, insula, OFC, temporal cortex, lateral PFC, and medial PFC	Investigated correlations of lifetime joints and age of onset with graph theory measures in regions where users and controls differed. Later age of onset was more strongly associated with global processing efficiency. Correlations with lifetime joints were not significant.
Van Hell et al. (2010)	14(1)/ 13(2)	24.0/24.0, adult	614 joints/year	NR	≥ 1 week	No	MID reward anticipation reward feedback	WB + ROI in R & L NAc	Money	Anticipation WB: ↓ NAc, caudate, L putamen, R IFG, R medial PFC, SFG, L cingulate, L occipital cortex ↑ MTG, R cuneus, R PHCG ROI: ↓ R NAc, L NAc (trend) Feedback WB: ↓ L FFG, MTG, occipital cortex, R	Additional comparisons between cannabis and tobacco users, not reported here.

										PCC, R cingulate, R MFG, R claustrum, R postCG, R IPL, R STG ↑ L MTG, L postCG, L PHCG, IFG, putamen, precuneus, cingulate, R medial PFC, R caudate, R preCG, R occipital cortex ROI: ns	
Yip et al. (2014)	20(0)/ 20(0)	26.7/29.2, adult	16.15/20.14 days/ month (did/did not achieve abstinence)	13.38/ 14.14 (first use, did/did not achieve abstinence)	NR	No	MID reward anticipation reward feedback	WB + ROI in R & L VS	Money	Anticipation: ns Feedback WB: ↓ parietal lobe, PCL, postCG, preCG, SMA, primary somatosensory cortex ROI: ns	Includes additional comparisons between users who achieved abstinence after treatment and users who did not, see original paper for results.
Zimmermann et al. (2019)	22(0)/ 24(0)	23.9/23.7, adult	27.91 days/ month	15.14 (first use)	30 days	Groups were matched	Inter-personal pleasant touch paradigm	WB Pleasantness ratings	Pleasant touch	WB ↓ R putamen Pleasantness: Users < controls	MRI results are for the female > male contrast, for which controls had greater activity, and users had lower activity. Higher lifetime use was associated with larger decrease in activity for female > male. Correlations

with abstinence and withdrawal were not significant.
Non-MRI results are for a t-test of group difference in score increase from male to female touch. A mixed fully factorial ANOVA did not yield any significant group effects. Correlation was not significant for withdrawal, and not reported for abstinence and lifetime use.
There was less than 80% power to detect a large effect for the pleasantness ratings.

* Reported for the combined sample.

**Values at baseline (longitudinal study)

Note. Up-arrows and down-arrows indicate whether users had higher or lower activity, respectively, in the given area relative to controls.

Abbreviations. As in Table 1a.

Brain regions: ACC – anterior cingulate cortex, CB – cerebellum, FFG – fusiform gyrus, HC – hippocampus, IFG – inferior frontal gyrus, IPL – inferior parietal lobe, ITG – inferior temporal gyrus, MFG – middle frontal gyrus, MTG – middle temporal gyrus, NAc – nucleus accumbens, OFC – orbitofrontal cortex, PCC – posterior cingulate cortex, PCL – paracentral lobule, PFC – prefrontal cortex, PHCG – parahippocampal gyrus, postCG – postcentral gyrus, preCG – precentral gyrus, SFG – superior frontal gyrus, SMA – supplementary motor area, STG – superior temporal gyrus, VS – ventral striatum

Tests & tasks: MID – Monetary Incentive Delay Task

Other: fMRI – functional magnetic resonance imaging, L – left, MDD – major depressive disorder, PPI – psychophysiological interaction, R – right, ROI – region of interest, SEM – structural equation modelling, WB – whole-brain

Table 2a. Acute behavioural studies.

Author (year)	**Participants** *n* (females)	**Age** Mean age in years, group	**Exposure**	**Use frequency** Mean, unless otherwise stated	**Duration of abstinence** Mean, unless otherwise stated	**Measure**	**Reward type**	**Results**	**Comments**
De Bruijn et al. (2017)	10(0)	23.4, adult	(1) 4 mg THC + 1 mg top-up (2) 25 mg CBD + 10 mg top-up (3) Placebo	4-52 days/year	≥ 2 weeks	Taste reactivity task (liking and sweetness)	Food	ns	Includes a number of additional tasks not reported here.
Lawn et al. (2016) [acute]	16(9)	26.2, adult	(1) 8 mg THC + 50 % top-up (2) 8 mg THC + 10 mg CBD + 50 % top-up (3) Placebo	8.06 days/month	≥ 24 hours	EEfRT SHAPS	Money	EEfRT: THC was associated with (a) lower likelihood of making a high-effort choice at low probability relative to placebo, and (b) increased sensitivity to magnitude changes at low probability relative to THC+CBD and (marginally) placebo SHAPS: ns	

Abbreviations. As in Tables 1a and 1b.
Other: CBD – cannabidiol, mg – milligram, THC - Δ^9-tetrahydrocannabinol

Table 2b. Acute neuroimaging studies.

Author (year)	**Participants** *n* (females	**Age** Mean age in years users/ controls, group	**Exposure**	**Use frequency** Mean, unless otherwise stated	**Duration of abstinence** Mean, unless otherwise stated	**Measure**	**Analysis method**	**Reward type**	**Results**	**Comments**
Freeman et al. (2018)	16(8)	26.3, adult	(1) 8 mg THC (2) 8 mg THC + 10 mg CBD (3) Placebo	8.06 days/ month	19.25 days	Music listening	Large ROI created from previous meta-analysis PPI in seed regions with drug effects Pleasure ratings	Music	ROI: ↓ Auditory cortex, R HC/PHCG, R VS, R amygdala during THC PPI: ↑ R VS with auditory cortex during THC+CBD compared to THC Pleasure ratings: ns	Task included listening to music and scrambled sound. Correlations of a) years of use and b) days per month of use with clusters showing drug effects and pleasure ratings were not significant.
Jansma et al. (2013)	11(0)	21.2, adult	(1) 6 mg THC + 1 mg top-up every 30 min (2) Placebo	22.6/23.5 days/year (non-nicotine dependents / nicotine dependents	≥ 2 weeks	MID reward anticipation reward feedback	ROI in caudate + putamen (combined), and NAc	Money	ns	Includes a nicotine-dependent comparison group. This group showed reduced activity in the NAc during reward anticipation after THC administration. See paper for full results. Main effect of condition within non-nicotine dependents was not significant. Reward*condition was not reported within non-nicotine dependents, but

										graphical representations suggest that this effect was not significant.
Van Hell et al. (2012)	11(0)	21.7, adult	(1) 6 mg THC + 1 mg top-up every 30 min (2) Placebo	17.9 days/year	≥ 2 weeks	MID reward anticipation reward feedback	ROI for regions with task-effects in either condition	Money	Anticipation: ↑ R OFC Feedback: ↓ R SFG	For feedback, THC reduced activity for both hits and misses in L IPL and ITG. THC also reduced signal change for misses in the PCC and OFC. All individual ROI effects were non-significant after correction for multiple comparisons.

Note. Up-arrows and down-arrows indicate whether brain activity was higher or lower, respectively, in active drug (THC) relative to placebo conditions.
Abbreviations. As in Tables 1a, 1b, and 2a.

Box 1 | **Task explanations**

Card Guessing Task: This task is completed in the fMRI scanner. Participants are instructed to guess whether the value of a visually presented card is greater than or less than 5, with possible values ranging from 1 to 9. Each trial begins with the presentation of a blank card, followed by a cue indicating whether the trial is a win (upward facing arrow) or loss trial (downward facing arrow). This is the anticipation interval. Following this is the feedback interval, in which the outcome (monetary win, loss, or no outcome) is displayed. (Casement, Shaw, Sitnick, Musselman, & Forbes, 2015)

Card Playing Task (CAPT): Participants are shown a deck of cards, and asked to turn over one card at a time. Each card carries either a monetary win or loss. There is a high rate of rewards during initial trials of the task, but as the game progresses, continued responding is followed by monetary loss. Participants are instructed to play until they decide to stop, with number of cards played indicating perseverative behaviour/reward learning. (Newman, Patterson, & Kosson, 1987)

Coin Toss Task: This task is completed in the fMRI scanner. Participants are instructed to guess whether a simulated coin flip will be "heads" or "tails". They indicate their guess by pressing a button, and are subsequently shown whether they have incurred a monetary win or loss. In the current version of the task, the coin-flip trials were alternated with perceptual motor control trials, in which participants were shown to blank coins with instructions to press either the left or the right coin. (Acheson et al., 2015; Hariri et al., 2006)

Effort Expenditure for Reward Task (EEfRT): Participants are told they can win a monetary reward by performing button-presses on a computer. On each trial, they are given the option between a low-effort, low-reward choice, and a high-effort, high-reward choice. Actual reward receipt is determined probabilistically, with a low (12%), medium (50%), or high (88%) probability. Important predictors are probability, magnitude, and effort (speed/number of button-presses required) level. (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009)

Interpersonal Pleasant Touch Paradigm: This task is completed in the fMRI scanner. Participants are introduced to a male and female experimenter before the scanning session. Whilst in the scanner, they are shown photographs of the male or female experimenter indicating three conditions: In the 'HOME' condition the experimenter is standing at 2 m distance, in the 'CLOSE' condition the experimenter is standing close to the participant, and in the 'TOUCH' condition the experimenter administers repeated soft touch to the shin of both legs of the participant. Participants rate perceived pleasantness after 'CLOSE' and 'TOUCH' trials. (Scheele et al., 2014)

Mood Rating Task: Participants perform a spatial delayed response task (adapted from Glahn et al., 2002), with two feedback conditions (reward, baseline) and three levels of difficulty. In the reward condition, correct responses earn a monetary reward, which increases with level of difficulty. Participants rate their momentary mood on a scale from 1 (bad) to 5 (good) at baseline, and after each difficulty block in each condition.

Monetary Incentive Delay Task (MID): This task is completed in the fMRI scanner. Participants are told they can win, or avoid losing a monetary reward depending on the speed of their responses. At the start of each trial, a cue is presented indicating the incentive type (win, loss, or neutral/no-outcome), and in some versions, reward magnitude. This is followed by a delay, constituting the reward anticipation interval. Following this a target is presented, and participants press a button as fast as they can. Finally, the outcome (win, loss, no outcome) and win/loss magnitude are presented, constituting the reward feedback interval. (Knutson, Westdorp, Kaiser, & Hommer, 2000)

Box 1 | **Task explanations** (continued)

Music Listening Paradigms: These tasks are performed in the fMRI scanner. (1) Ford et al. (2014): Participants listen to preferred instrumental music, selected by themselves or from bank based on previous participants. They also listen to neutral instrumental music, selected from a bank of other participant's preferred music. (2) Freeman et al. (2018): Participants listen to excerpts of standard instrumental classical music and scrambled sound. Scrambled excerpts retain the same distribution of pitch and loudness, and the same spectral information as the classical music excerpts. (adapted from Menon & Levitin, 2005)

Probabilistic Reward Task: This task uses abstract faces with short (8 mm in the current study) and long (9 mm in the current study) mouths as stimuli. Participants are instructed to make quick guesses about whether they are presented with the short or long mouth, and can sometimes win money if guessing correctly. One of the stimuli/mouths (the 'rich' stimulus) is reinforced three times more frequently than the other (the 'lean' stimulus). The main outcome of this task is response bias, which indexes the participant's bias towards the more frequently reinforced stimulus. (Pizzagalli, Jahn, & O'Shea, 2005)

Progressive Ratio Task (PRT): Participants are presented with two mutually exclusive options: a progressive-ratio (PR) reinforcement schedule and a fixed time (FT) reinforcement schedule. In the current version of the task, the reinforcer and the number of responses required increased with each trial in the PR schedule. In the FT schedule, reinforcement magnitude was identical to that earned on the last completed PR trial, and the time interval for each delivery was either the time required to complete the last PR, or 120 seconds (whichever was larger). Rewards were monetary, and main outcomes were largest PR completed, and earnings derived from the FT option. (adapted from Cherek, Lane, & Dougherty, 2002)

Taste Reactivity Task: In the version used by de Bruijn et al. (2017), participants were given seven 20 ml chocolate milk drinks differing in sugar concentration, and asked to rate perceived sweetness intensity and liking of each drink. They also completed a control task, in which they were asked to rate the greyness of seven shades of grey.