NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

MEDICAL SCHOOL

DEPARTMENT OF PSYCHIATRY

DOCTORAL DISSERTATION

THE STUDY OF THE EFFECT OF REWARD ON COGNITIVE MECHANISMS OF DECISION PROCESSING IN PATIENTS WITH SCHIZOPHRENIA AND CHRONIC CANNABIS USERS

Μελέτη της επίδρασης της ανταμοιβής στους νοητικούς μηχανισμούς λήψης απόφασης σε ασθενείς με σχιζοφρένεια και χρήστες κάνναβης

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MSc Clinical Psychology

2022

DOCTORAL DISSERTATION

The effect of reward on cognitive mechanisms of decision processing in patients with schizophrenia and chronic cannabis users

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This dissertation was supported by the Greek state through IKY (State Scholarships Foundation), Unit of Foreigners and Cultural Exchanges.

ACKNOWLEDGEMENTS

The research for this doctoral dissertation was carried out at the department of Psychiatry during the years 2015-2022. The project was carried out in collaboration with the laboratory of Sensorimotor Control under Professor Nikolaos Smyrnis, at the University Mental Health Research Institute (EPIPSY). In order to complete this research, I received a scholarship from the Greek State Scholarship Foundation (IKY), for which I am ceaselessly grateful.

I would also like to thank my three-member monitoring committee: Nikolaos Smyrnis, Nikolaos Stefanis and Charalambos Papageorgiou, with a special thanks to Nikolaos Smyrnis who provided rounded guidance and support during this time.

Thirdly, a huge thank you goes out to my family and friends who have endured the ups and downs of this journey almost as much as I have. I could not have made it this far without their support.

Finally, the contribution of this work would not have been possible without all of the individuals who volunteered to participate in this research and for this I am forever grateful.

ABSTRACT

Chronic cannabis use and schizophrenia are both thought to affect reward processing. While behavioural and neural effects on incentive processing have been investigated in both populations, their interaction has not been studied, although chronic cannabis use is common among schizophrenia patients. In the present study eighty-nine participants divided into four groups (control chronic cannabis users and non-users; schizophrenia patient cannabis users and non-users) performed a two-choice decision task, preceded by incentive cues (high/low reward/punishment or neutral), while being scanned using functional magnetic resonance imaging. Reward and punishment anticipation resulted in activation of regions of interest including the thalamus, striatum, amygdala and insula. Chronic cannabis use and schizophrenia had opposing effects on reward anticipation sensitivity. More specifically control users and patient non-users showed faster behavioural responses and increased activity in anterior/posterior insula for high magnitude cues compared to control non-users and patient users. The same interaction pattern was observed in the activation of the right thalamus for reward versus punishment cues. This study provided evidence for the interaction of chronic cannabis use and schizophrenia on reward and punishment processing and highlights the need for future research addressing the significance of this interaction for the pathophysiology of these conditions and its clinical consequences.

Keywords:

psychosis, mesolimbic pathway, insula, anterior, posterior, thalamus, reaction time, monetary incentive delay (MID), dopamine, functional magnetic resonance imaging (fMRI), incentive, region of interest**.**

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CHAPTER 1

1. General Introduction

1.1 . Cannabis, its use and effects

Cannabis is the most widely used drug worldwide. Research carried out by the United Nations Office of Drugs and Crime in 2021 estimated that almost four per cent of the global population, equating to around 200 million people aged 15-64 used the substance in 2019; a substantial increase over the previous decade. With a growing trend toward legalisation in countries across the globe, cannabis use is becoming increasingly more acceptable within society and prevalence across the world's population is likely to further increase. The behavioural and neurophysiological effects of cannabis use are diverse and not yet fully understood; nevertheless the substance has been used in Western medicine since the 19th century (Zuardi, 2006), and more recently it has been used as a treatment for neuropathic pain, spasticity in multiple sclerosis and nausea and vomiting in patients receiving chemotherapy, with varying efficacy (Allan et al., 2018), and alongside aversive effects including dizziness, confusion, sedation and dissociation. Conversely, ingestion of cannabis has been found to have both acute and chronic effects on memory, attention, psychomotor and executive functioning as well as decision-making (Broyd et al., 2016).

At least 120 cannabinoids have been isolated from the cannabis sativa plant to date (ElSohly et al., 2017), each with their own unique phytochemistry. With regards to potential positive and negative effects of cannabis use, interest has been given primarily to two of the substance's most abundant constituents: Δ^9–tetrahydrocannabinol (THC); this main psychoactive ingredient, has been found to be responsible for acute positive and negative psychotic symptoms, anxiety, dysphoria and sedation (Martin-Santos, 2012). Conversely, cannabidiol (CBD) is non-psychoactive, and has been found to have anxiolytic (Crippa et al., 2011; Moreira et al., 2006) and antipsychotic properties (Iseger & Bossong, 2015; Schubart et al., 2014). There is also some evidence that CBD may inhibit some acute effects of THC including paranoia and memory impairment (Englund et al., 2013).

1.2 Chronic cannabis use and schizophrenia

As previously stated, THC has been shown to induce acute psychotic symptoms, but there are numerous other associations between the use of cannabis and the presence of schizophrenia. It has long been known that schizophrenia has a genetic element (Gottesman, 1991; Tienari, 1991; Owen, 2012) with an overall heritability estimate of 80-85% (Cardno & Gottesman, 2000). Such findings led to research into genetics involved in the disorder. In 2014, a genome-wide association study (GWAS), carried out by the Schizophrenia Working Group of the Psychiatric Genomics Consortium identified 128 single nucleotide polymorphisms (SNPs) across 108 loci that can be considered associated with schizophrenia.

While the concordance rates within families is high, it cannot fully account for the onset of disorder, even in monozygotic twins. For this reason research has looked to the impact of environmental factors. Genetically susceptible individuals may or may not subsequently develop schizophrenia in the presence or absence of certain environmental factors including childhood neglect and abuse (Read et al., 2005), migration (Bourque et al. 2011; Cantor-Graae & Selten, 2005) and urbanicity (Kelly et al., 2010), amongst others including cannabis use.

Longitudinal follow-up studies have demonstrated correlations between cannabis use and subsequent schizophrenia onset. A study of 50,087 Swedish conscripts, carried out by Zammit et al., (2002) measured self-reported substance use and later onset of schizophrenia between 1970 and 1996, finding a higher incidence of schizophrenia onset with increasing frequency of cannabis use that could not be attributed to the use of other substances. A second study in the Netherlands by Ferdinand et al., (2005) reported a bidirectional vulnerability between cannabis use and psychosis, replicating the finding of an increase in psychotic symptoms following onset of cannabis use, as well as displaying that individuals

displaying symptoms of psychosis are more likely to use cannabis. A further birth cohort study carried out in New Zealand, replicated these findings, highlighting the additional importance of age of first use, with a higher incidence of schizophreniform disorder onset among those who began using cannabis before the age of 15, as opposed to 18 (Arseneault et al., 2002).

Indeed, there is substantial evidence to suggest that the age of first exposure to cannabis use may increase vulnerability to subsequent schizophrenia onset. A longitudinal study carried out by Fergusson et al., (2003) followed individuals over a twenty-one year period and reported that individuals confirmed to display symptoms of cannabis use disorder at age 18 were twice as likely to display psychotic symptoms compared to those who did not. Psychotic symptoms preceding cannabis dependence were controlled for to eliminate the possibility that cannabis use was driven by psychosis. A further longitudinal study tested participants for cannabis use and psychotic symptoms and confirmed that non-affective psychosis, delusions and hallucinations were more prevalent in individuals who reported longest duration since first cannabis use. Results remained significant within sibling pairs, reducing the likelihood that the effect may be due to confounding genetic factors (McGrath et al., 2010). It has been suggested that the younger the age of first use, the higher the vulnerability to developing psychotic symptoms, due to neuronal networks, including the endocannabinoid system (Schneider, 2008) still being under development. Furthermore, other neurotransmitter systems including dopamine are under development during this period (Wahlstrom et al., 2010). Exposure to exogenous cannabinoids could interfere with such complex reorganisation of neuronal systems, contributing to the subsequent development of schizophrenia.

Research carried out by Di Forti et al., (2009) did not confirm any differences between age of first use and later onset of psychotic symptoms. However this study did report

that first-episode psychosis patients were more likely to have used cannabis for a longer duration and with a higher frequency compared to a non-psychosis control group from the general population. Furthermore, it was reported that patients were more likely to have used sinsemilla, or 'skunk' than controls. Sinsemilla is a highly potent strain of cannabis that has been reported to contain up to four times more THC than marijuana or resin (Hardwick & King, 2008; Potter et al., 2008; Potter et al., 2018).

Not only has the chronic use of cannabis been found to increase the likelihood of developing schizophrenia, but individuals with schizophrenia have also been found to display a higher incidence of cannabis use. Termed, the self-medication hypothesis, it has been said that individuals who seek substances do so to relieve stress and that the type of substance that a person uses is specific to their psychological symptomatology (Khantzian & Albanese, 2008). In support of this hypothesis, research has demonstrated that the self-medication of cannabis among individuals with schizophrenia may alleviate some negative symptoms of the disorder. In 1992, Peralta and Cuesta assessed the differences in positive and negative symptoms of patients with and without concurrent cannabis use and reported an improvement in negative symptoms, particularly alogia among patients who used cannabis, while positive symptoms were somewhat increased. Bersani et al., (2002) extended these findings on a sample of patients in Italy, reporting a reduction in affective-flattening, avolition and anhedonia in cannabis users compared to non-users, with an overall total reduction in negative symptomatology.

Despite such a reduction in negative symptoms, patients who use cannabis have generally been found to have worse prognosis and functional outcome in comparison to non-users; having been found to be at risk of relapse (Schoeler et al., 2016), and to have an increased number of hospital admissions and prescribed medication (Patel et al., 2016). Furthermore, an eight-year follow-up study by González-Pinto et al., (2011) reported that

participants who had stopped using cannabis following a first psychotic episode had improved functional outcome compared to current users and non-users. Other follow-up studies have also reported enhanced outcome in individuals who stop using cannabis (Clausen et al., 2014; Weibell et al., 2017; Setién-Suero et al., 2019).

1.3 Cognition in chronic cannabis use and schizophrenia

A systematic review carried out by Broyd et al., (2016) found ingestion of cannabis in healthy individuals to acutely affect cognition in a range of domains, with strong evidence for an impairment in verbal and working memory, attention and psychomotor function, and moderate evidence for a deficit in inhibition. A further meta-analysis of acute effects of partial cannabinoid receptor one (CB_1) agonists including cannabis and THC, reported small to moderate impairments in verbal learning and memory, working memory, executive functioning, processing speed, impulsivity and attention (Zhornitsky et al., 2021).

Broyd et al. (2016) also assessed evidence of chronic use, reporting a deficit in verbal learning and memory, attention as well as attentional bias. The researchers however, reported weak evidence for a deficit in psychomotor function. Some studies have however, reported an impairment in this domain. Lisdahl & Price (2012) assessed the cognitive ability of long-term users on a range of measures and reported deficits in psychomotor speed as well as attention and cognitive inhibition. Another study also reported a deficit in psychomotor speed in current heavy cannabis users, as well as immediate and delayed memory and overall IQ (Fried et al., 2005). Conversely, while reporting deficits in a range of cognitive domains including working and verbal memory at baseline and two-year follow-up, Becker et al., (2018), found improved processing speed among young adult chronic users of cannabis whose use began before age seventeen. Reports of no differences in reaction time (RT) between users and non-users has also been reported (Whitlow et al., 2004).

The finding of a strong impairment of attentional bias in chronic users is of interest, as this denotes that cannabis-related cues have become increasingly salient, in turn eliciting a stronger craving response as well as elevated pleasure over non-drug cues (Berridge & Robinson, 2003; Cousijn et al., 2013; Field et al., 2006).

Chronic users of cannabis have been found to have a generalised impairment in cognitive performance as measured by a composite score (D'Souza et al., 2020) as well as decreased error awareness as measured by decreased blood oxygen level dependent (BOLD) response in anterior cingulate cortex (ACC) and right insula in response to errors (Hester et al., 2009). Other reviews and meta-analyses have stated the possibility that cognitive impairment may cease after abstinence (Scott et al., 2018; Broyd et al., 2016).

The pattern of cognitive deficits that exists in chronic users of cannabis is similar to those observed in schizophrenia patients. This deficit often occurs prior to disorder onset and is a strong indicator of social and functional outcome (Cornblatt et al., 1999; O'Carroll., 2000). Premorbid cognitive domains found to be impaired are IQ (Khandaker et al., 2011) and poor academic achievement (MacCabe et el., 2008; Fuller et al., 2002), however a meta-analysis reported that while a premorbid deficit was present for IQ and motor function, poorer academic achievement was not related to subsequent disorder onset (Dickson et al., 2012). During this phase, deficits in verbal ability (MacCabe et al. 2013) and attention (Cannon et al., 2006) have been reported, suggesting that such a cognitive impairment exists before disease onset.

After the first onset of symptoms and during disorder progression, cognitive impairment continues to be present, with evidence of a more generalised deficit across domains (Keefe & Harvey, 2012; Heinrichs & Zachzanis, 1998). Furthermore, similar to chronic cannabis users, error-monitoring hypoactivity in ACC has also been demonstrated

(Carter et al., 2001). Research has suggested that a core feature of this cognitive deficit is a slowing down of processing speed (Dickinson et al., 2007) with research consistently demonstrating an increase in RT across different cognitive domains (Cadenhead, 1997; Vinogradov et al., 1998; Nuechterlein, 1977). There is also evidence to suggest that this generalised cognitive deficit is stable across the course of disease and stages of life (Goldberg et al., 1993).

While this deficit is a common feature of the disorder, there are some individuals who do not display this characteristic. A cohort of schizophrenia patients have been reported to display a sparing of cognitive function (Palmer et al., 1997). More recent research has suggested the comorbid use of cannabis in schizophrenia patients may be responsible for this sparing. A plethora of research has suggested that schizophrenia patients who also have a history of cannabis use demonstrate enhanced cognitive functioning in comparison to those without a history, in a wide range of different domains and tasks (DeRosse et al., 2010; Løberg and Hugdahl 2009; Potvin et al., 2008; Rabin et al., 2011; Yücel et al., 2012; Coulston et al., 2007; Rodríguez-Sánchez et al., 2010; Jockers-Scherübl et al., 2007). Some research has argued that this enhanced cognition could be the consequence of improved premorbid functioning in cannabis-using patients (Sevy et al., 2001; Rodríguez-Sánchez et al., 2010). Others have suggested that a higher frequency and recency of cannabis use may be attributed to improved cognition (Schnell et al.. 2009; Coulston et al.. 2007).

Some research has found previous use of cannabis, followed by abstinence, to be the factor most associated with improved cognitive ability (Rabin et al., 2013; Rabin et al., 2017). However, it has been said that impaired cognition seen in current users may be explained by residual intoxication effects, reflecting the acute impact that cannabis is known to have on cognition (Løberg and Hugdahl 2009). According to Yücel et al., (2012), the spared neurocognition seen in some schizophrenia patients may represent a sub-group of

patients who developed the disorder after early initiation of cannabis use. In support of this, some studies have reported enhanced cognitive functioning in those patients who began using cannabis earlier in adolescence (Hanna et al., 2016; Jockers-Scherübl et al., 2007). Interestingly, this latter study reported improved functioning in patients who began using before age 17, while the opposite was true of healthy controls. As well as triggering an earlier schizophrenia onset, this early substance use may lead to improved performance in some individuals via a period of prolonged abstinence. It should be noted, that some studies have reported no differences in cognitive performance between users and non-users (de Vos et al., 2020; Sevy et al., 2007), however only very few have reported users to have worse performance than non-users (Mata et al., 2008).

It can be said that the majority of research points toward sparing of a cognitive deficit in schizophrenia patients who either have used or currently use cannabis. One explanation for this phenomenon is that cannabis may have a neuroprotective role which contributes to preserved cognitive functioning (Coulston et al., 2007). However given the findings of worse functional outcome of schizophrenia patients in users of cannabis, the argument for this is weak. Another explanation is that the use of cannabis impairs cognitive function in a way similar to that seen in an endophenotypic fashion in schizophrenia (Solowij & Michie, 2007), and that the neurobiological underpinnings of this deficit in both populations are similar. In vulnerable individuals, or after excessive exposure to THC, schizophrenia may be triggered, in the absence of a serious cognitive impairment (Løberg and Hugdahl 2009). This theory points toward a different pathway to schizophrenia, where disorder onset may not have occurred in the absence of exposure to cannabis.

1.4 Reward, punishment and its neural underpinnings

A reward is an environmental stimulus that an individual is willing to work to achieve, and punishment a stimulus that one strives to avoid. Behaviourally speaking, the receipt of reward increases the probability that a behaviour is repeated in the future, and punishment decreases the likelihood that the behaviour will continue. Over time, behaviours learned from receipt of reward or avoidance of punishment are likely to be repeated even in the absence of reward.

Rewards can be divided into primary and secondary categories. Primary rewards relate to physiological needs and experiences of the individual for example food, while secondary rewards are not directly linked to biological need, but some other incentive that one is motivated to receive, for example money or indeed anything that an individual finds pleasurable.

Berridge and Robinson (2003) have divided reward into three separable yet interlinked components: the ability to learn the consequences associated with stimuli, the hedonic response to the received reward and the motivation to learn and act to receive the reward. Put simply, there must be learning, liking and wanting. In the presence of reward, dopamine and glutamate are fired from the ventral tegmental area (VTA) to the amygdala, ventral striatum (VS) and pallidum, as well as prefrontal and insular cortices. Each of these areas plays a specific role in one or more of the three reward components, for example the VTA and amygdala are involved in motivation, while the VS and ventral pallidum are also linked to liking, and prefrontal and insula cortices have been linked to incentive learning (Berridge & Robinson, 2003). In reality, however, the mesocorticolimbic reward system is a highly sophisticated network, a reflection of its psychological components, whereby the integration of motivational, emotional and learning processes work together to form the

ability to perceive and process rewards within the environment. Both the endocannabinoid and dopaminergic systems have been found to influence the functionality of this pathway.

The endocannabinoid system is made up of CB_1 receptors and cannabinoid 2 (CB_2) receptors. The release of endocannabinoids activate these receptors which in turn modulate other neurotransmitters. The most abundant endogenous endocannabinoids are anandamide (*N*-arachidonoyl-ethanolamine; AEA) and 2-arachidonoyl-glycerol (2-AG). Furthermore the most common receptor in the central nervous system (CNS) are CB_1 receptors, which have been demonstrated to be of importance in a number of cognitive processes including learning (Acosta et al., 2017), memory (Morena & Campolongo, 2014) and reward processing (Sanchis-Segura et al., 2004; Solinas et al., 2008). The introduction of exogenous cannabinoids into the CNS has further implications for the functioning of the endocannabinoid system as a whole, as well as its interaction with other neurotransmitters. THC is an exogenous cannabinoid and has high binding affinity to both receptor types, however given the prominence of CB_1 receptors in the CNS, the influence of these receptors on the neurocognitive effects of THC is great. CB_1Rs are found extensively throughout the mesocorticolimbic pathway and play an important role in the processing of reward. There are high levels of CB_1 receptors in the striatum and lower levels in VTA (Herkenham et al., 1990; Tsou et al., 1998). That said, when injected directly into these regions of rat brains, THC has been found to have rewarding effects in both areas (Zangen et al., 2006). Agonists of CB_1 receptors can therefore be thought of as having a modulating effect on neuron activity within the VTA, indirectly influencing reward processing. Furthermore, a study by Sanchis-Segura et al., (2004) found that the deletion of CB_1 receptors in knockout mice resulted in reduced sensitivity to reward. As expected, exogenous cannabinoid agonists result in increased reward sensitivity and antagonists, reduced sensitivity. In rats, small doses of THC have been found to increase the appetitive response to sucrose, while decreasing aversive response to quinine

solution (Jarrett et al., 2005; Jarrett et al., 2007). Additionally, administration of AM251, an inverse agonist at CB_1 receptors had the opposite effect (Jarrett et al., 2007) suggesting the role of cannabis in increasing sensitivity to reward and decreasing sensitivity to punishment. Experiments with CB_1 knockout mice have also demonstrated a reduction in food consumption after restriction in comparison to non-knockout mice (DiMarzo et al., 2001) and increased anhedonia after mild chronic stress (Martin et al., 2002), further highlighting the importance of CB_1 receptors in the reward system.

There is evidence to suggest that THC interacts with the dopaminergic system, increasing its synthesis (De Fonseca et al., 1990), resulting in increased dopamine activity in the mesocorticolimbic pathway (Pistis et al., 2002; Melis et al., 2000). After administration of THC, dopaminergic transmission has been found to be increased in the human VS (Bossong et al., 2009). Furthermore, administration of rimonabant, a CB_1 receptor antagonist, the endocannabinoid system has been associated with reduced neuronal reward response (Horder et al., 2010).

The chronic use of cannabis, over time is associated with a reduction in dopaminergic activity, particularly in reward-related brain areas (Tanda & Goldberg, 2003). Desensitisation of the endocannabinoid system under prolonged exposure to cannabis may be responsible for this attenuation (Sim-Selley, 2003). A reduction in striatal dopamine release (van de Giessen et al., 2017), as well as synthesis capacity (Bloomfield et al., 2014) in chronic cannabis users has been reported, pointing toward a blunting of the dopaminergic system.

However, increases in VS dopamine release following THC administration, discussed above (Bossong et al., 2009), together with increased dopamine release in this area in response to non-drug reward cues (Schott et al., 2008) has led to the confirmed hypothesis

that chronic use of cannabis may result in hypersensitivity of the VS in response to all forms of reward (Nestor et al., 2010).

In schizophrenia, irregularities in the dopaminergic system have long been addressed, with a general consensus of elevated levels of presynaptic functionality (Howes et al., 2012). These increases have been found to result in reduced reward-related activity in the mesocorticolimbic pathway (Juckel et al., 2006a; Nielsen et al., 2012; Radua et al., 2015). Schizophrenia patients have also been found to display differences in the endogenous endocannabinoid system including in ACC (Zavitsanou et al., 2004) and nucleus accumbens (NAcc) (Ceccarini et al., 2013).

Research into the interactions of the endocannabinoid and dopaminergic systems between patient users and non-users remains scarce and inconclusive. Safont et al., (2011) reported no differences between first-episode users and non-users in dopamine 2 (D_2) receptor binding. While one study demonstrated increased CB_1 receptor binding for patient users compared to non-users in dorsolateral prefrontal cortex (Dean et al., 2001), others have failed to replicate this finding (Cerccarini et al., 2013; Ranganathan et al., 2016). These findings were however not the purpose of these latter studies.

Thus, differences in the neurobiology underpinning motivation and reward can be observed between chronic cannabis users, patients with schizophrenia and healthy controls, whereby the behaviour of these neurotransmitters in brain areas heavily involved in reward result in the differential behaviour and symptomatology experienced by these groups.

1.5. Monetary incentive delay and motivation in chronic cannabis use and schizophrenia

In humans, the monetary incentive delay (MID) task has been used to measure reward and punishment processing. Developed by Knutson et al. (2000) the task measures the behavioural and neural response of different stages of the reward process. Each trial consists

of a cue that informs the participant of the valence and/or magnitude of the upcoming reward, after which appears a target stimulus, to which the participant is asked to respond. Whether the reward is given or punishment avoided, is dependent on the reaction of the participant. Research on an MID task have yielded inconsistent results with some reports of no between-group differences of chronic users of cannabis and healthy controls (Enzi et al., 2015) during reward anticipation. However van Hell et al., (2010), reported hypoactivity in VS and caudate nucleus during reward anticipation in cannabis users, though the absence of group differences in VS activity between cannabis and nicotine users resulted in only attenuation of caudate nucleus being attributed to cannabis.

In contrast, Nestor et al., (2010) argue that chronic drug users may hold both a hyperactive mesolimbic circuitry in response to reward and a hypoactive frontocortical response to punishment avoidance, and that cannabis use may result in a heightened VS response to all forms of reward. Indeed, these researchers observed an increased BOLD response in the right VS for chronic users of cannabis in comparison to healthy controls, while no behavioural differences were observed. This response was further related to duration and frequency of use. The researchers propose that the use of cannabis sensitises the mesocorticolimbic system to all types of reward. As the authors state, it cannot be known that such hypersensitivity to reward is the direct result of chronic cannabis use. Alternatively, it may in fact be the case that sensitisation of the mesocorticolimbic circuitry is what drives some individuals to seek out cannabis as well as other rewards. Further to these differences in reward anticipation, the researchers reported a hypoactivity in insula cortex in response to loss and loss avoidance outcome.

Research using the MID task in schizophrenia patients has yielded more consistent results, indicating a general hypoactivation of striatum during reward anticipation (Li et al., 2018; Juckel et al., 2006a) as well as VTA and cingulate cortex (Nielsen et al., 2012). This

latter study used a sample of antipsychotic naïve patients and reported attenuation of VS during the reward anticipation phase to be correlated with positive symptomatology. A body of research has however found this attenuation to normalise in schizophrenia patients who are treated with atypical antipsychotic medication (Schlagenhauf et al., 2008; Juckel et al., 2006b) resulting in no between-group differences in comparison to healthy controls.

That said, the majority of research using this task in schizophrenia patients has investigated the correlations with negative symptomatology. Juckel et al., (2006a) reported attenuated activity in left VS during reward anticipation to be associated with higher ratings of general negative symptomatology, as measured by the Positive and Negative Syndrome Scale (PANSS), while other studies have reported a reduction in VS activity during reward anticipation to be associated with more severe apathy (Stepien et al., 2018; Simon et al., 2010; Kirschner et al., 2016).

Reward seeking and punishment avoidance are key motivational processes. Results from MID studies can therefore be explained by differences in motivation in both chronic users of cannabis and schizophrenia patients.

Chronic use of cannabis has long been linked to amotivation. The term cannabis amotivational syndrome was first coined in 1968 (McGlothilin & West, 1968; Smith, 1968); based on clinical observations, the syndrome is related to reduced concentration and ability to master new material, difficulty following routine as well as an apathetic state. The involvement of THC in the activation of neural reward centres via irregularities in neurotransmission, discussed above, highlights its role in motivation and reward processing.

Since it is known that dopamine plays an important role in reward-based learning (Berridge & Robinson, 1998) and chronic cannabis use has been found to be associated with reduced dopamine release and synthesis, particularly in the striatum (van de Giessen et al.,

2017; Bloomfield et al., 2014), one explanation that remains paramount is that a reduction in dopaminergic functioning may underlie the amotivational state. The reward deficiency syndrome is a proposed theory whereby chronic use of a drug, in this case cannabis, alters striatal reward functioning, which may then only be normalised by the continued use of cannabis, and is a proposed model of addiction. Cannabis itself has become the sole reward worth working for and other rewards fail to reach the same intrinsic value (Volkow et al., 2016). Known as the incentive salience hypothesis, cannabis and its cues now hold increased motivational value in comparison to other reinforcers.

Studies have demonstrated decreased motivation in chronic cannabis users across self-report and interview studies, as well as performance based and neuroimaging measures (Pacheco-Colón et al., 2018). Paule et al., (1992) reported chronic cannabis exposure in rhesus monkeys to be associated with an amotivational-like syndrome which was present for two to three months following last exposure, suggesting the medium to long-term effects that the substance can have on this deficit. Amotivation may however be a characteristic of cannabis dependence as opposed to chronic cannabis use per se (Nestor et al., 2010).

Akin to cannabis use, one key negative symptom observed in patients with schizophrenia is amotivation. This feature of the disorder has been highlighted as critically important in predicting patients' functional outcome (Foussias & Remington, 2010). Various explanations for the motivational impairment in schizophrenia have been proposed. The most simple of these is that the patient does not experience enjoyment in typical activities. Indeed anhedonia, has long been defined as a feature of schizophrenia and is listed in the diagnostic criteria of the disorder. However, it has been said that schizophrenia patients are more emotionally active than first presumed (Myin-Germeys et al., 2000), provoking research into the underlying mechanisms behind anhedonia and amotivation. One field of research has investigated the notion that patients display a deficit in reinforcement learning, in that

feedback information following rewarding stimuli is not adequately updated to modify behaviour and optimise future receipt of reward. Indeed, research has established that schizophrenia patients display a deficit in utilising feedback in order to modify the behavioural response and that this deficit may be restricted or more severe in those with increased negative symptomatology (Waltz & Gold, 2007; Waltz et al., 2011). This pattern is reflected in neural activation, as patients with more severe negative symptomatology display greater reductions in VS activity in response to reward anticipation (Waltz et al., 2010). Whether such learning is indeed disrupted in schizophrenia remains largely unclear, with many studies reporting somewhat undisturbed procedural learning in different tasks including serial RT (Green et al., 1997) and Tower of Hanoi (Goldberg et al., 1990), among others (Gold et al., 2009; Clare et al., 1993). Elsewhere, studies have found impaired procedural learning in patients, reflected in differential neural activation (Kumari et al., 2002) in comparison to controls. A further argument in relation to a deficit in reinforcement learning has stated that patients may display impairments in positive outcome learning, but an undisturbed ability to learn from negative ones (Strauss et al., 2014), therefore patients are able to avoid punishments but less able to modify behaviour to receive rewards.

It has also been suggested that patients with schizophrenia may display a deficit in value representation. This refers to the ability to accurately assess, maintain and update the mental representations of value (Barch & Dowd, 2010). A crucial cortical region involved in this construct is the orbitofrontal cortex. This region enables the analysis of an outcome's value, the extent to which this outcome satisfies current motivational requirements, as well as comparing this outcome against alternatives (Wallis, 2007). In order for this to be achieved, information needs to be continually stored and updated, encompassing working memory. There is evidence to suggest that individuals with schizophrenia display deficits in this domain as indicated by research on measures including the Iowa Gambling (Shurman et al..

2005; Lee et al., 2007) and set-shifting tasks (Pantelis et al., 1999; Tyson et al., 2004; Ceaser et al., 2008). Additional studies have highlighted deficits in value representation via tasks of graded valence, where patients self-reported more inconsistent preferences (Strauss et al., 2011), and were unable to discriminate highly graded from mildly graded valence. Similarly, schizophrenia patients have also been found to display self-report patterns similar to this, on a delay-discounting task, reporting a preference for small, immediate rewards over larger delayed rewards (Heerey et al., 2007).

A final element underlying goal-directed behaviour is effort computation. This refers to the assessment of the amount of effort that is required to achieve the available reward and whether the reward outweighs the cost of the behaviour required to achieve it. Dopaminergic function has been shown to play an important role in this assessment. In a study by Wardle et al., (2011), healthy controls were administered d-amphetamine, a dopamine agonist and observed an increase in willingness to exert effort in order to obtain rewards, with a marked increase when the probability of receiving that reward was low. Additionally, the ACC has been highlighted to be of specific importance in effort-based decision making (Walton et al., 2009), an anatomical region that has been associated with reduced functionality during cognitive tests in schizophrenia (Kerns et al., 2005). While the research into dopaminergic abnormalities in schizophrenia is vast, variable and inconclusive, one study reported that mice with elevated levels of postsynaptic D_2 receptors exhibited decreased willingness to work for rewards (Ward et al., 2012); schizophrenia patients have also been found to display this same increase in D_2 receptor levels (Fusar-Poli & Meyer-Lindenberg, 2013a; Fusar-Poli & Meyer-Lindenberg, 2013b). Furthermore, behavioural studies investigating effort-based decision-making have reported that schizophrenia patients were more likely to choose a low-effort condition that would result in a smaller reward, than a task requiring more effort that would result in a larger reward (Gold et al., 2013), and that such effects were increased in

individuals with higher negative symptomatology (Fervaha et al., 2013a; Fervaha et al., 2013b). Evidence for different aspects of reward processing underlying amotivation in schizophrenia and their relation to negative symptomatology highlights the complex nature of defining the specific neurobiological processes linked to a lack of goal-directed behaviour in schizophrenia.

Symptom patterns have been found to vary between patient-users and non-users which may therefore affect reward processing between these two patient subgroups. A meta-analysis investigating symptomatology patterns in schizophrenia patients with and without comorbid cannabis use reported patient-users to display a reduction in negative symptoms (Talamo et al., 2006). It has been suggested that these individuals may be more socially competent than their non-using counterparts, reflected in their ability to obtain illicit substances. Superior premorbid adjustment has also been reported among patients with comorbid substance use (Arndt et al., 1992). However, negative symptoms worsen over time in comorbid patients, resulting in poorer functional outcome, as discussed above (Volkow, 2009).

A large-sample study of 1434 patients investigated the relationship between cannabis use and motivation in schizophrenia patients (Bahorik et al., 2017). This study assessed substance abuse at baseline and six-month follow-up, reporting lower levels of intrinsic motivation in users compared to non-users at both time points. This study also found reductions in use at follow-up to be associated with higher levels of intrinsic motivation. These findings were true of both alcohol and cannabis. Furthermore, higher relapse rates and reduced motivation to alter using habits have been reported in using patients compared to using healthy controls (Horsfall et al., 2009).

However, the cannabis-schizophrenia comorbidity is thought to be bidirectional. Negative symptoms are associated with a reduction in dopaminergic activity (Howes et al. 2015) and acute exposure to cannabis can increase dopaminergic function, temporarily improving negative symptomatology, including amotivation. It may therefore be the case that patients seek out cannabis in an attempt to alleviate the symptoms of the disorder.

There is some evidence to suggest that schizophrenia patients use cannabis as a means to increase motivation. Cassidy et al., (2014a) investigated motivation to exert effort to view pleasant stimuli in patients with or without concurrent cannabis use, as well as healthy controls with the same cannabis-using habits. It was reported that all patients were significantly less likely to be motivated to view pleasant stimuli, in comparison to controls, and this lack of motivation was predictive of cannabis use over the following month in patients but not controls. In another study, Cassidy et al., (2014b) found that patients who exhibited a blunted late-positive event-related potential (LPP) response to pleasant stimuli also predicted cannabis use at one month follow-up. Thus, in both studies, the patients with worse amotivation were more likely to subsequently use cannabis.

One study has investigated the neurological underpinnings of how cannabis use may serve to target reward-processing disruption in schizophrenia. Fischer et al., (2014) used resting-state functional connectivity to measure brain reward circuitry connectivity of patients and controls, reporting reduced connectivity between NAcc and prefrontal cortex in patients. After administration of cannabis and oral THC, the connectivity of these regions was increased in patients, supporting the notion that patients may use cannabis as a way to enhance reward functioning and motivation.

While cannabis use may acutely alleviate amotivation, the fact that chronic exposure to the substance results in reduced dopaminergic functioning, the continued use of this substance may exacerbate the reward processing deficit.

1.6. Summary

Cannabis consumption has been demonstrated to cause transient psychosis as well as cognitive impairment, features that are consistently observed in schizophrenia. When used chronically, use of the substance can lead to amotivational syndrome and induce psychotic disorders including schizophrenia, in some at-risk individuals. Neurobiological differences in comparison to healthy non-using controls have been observed in these populations including functionality of the endocannabinoid and dopaminergic systems, which in turn lead to altered functioning of the mesocorticolimbic reward circuit, resulting in difficulties in the processing of rewards. The prevalence of cannabis use in the schizophrenia population is high and cognitive impairment among patient-users is thought to be lower than that of non-users. It may be the case that schizophrenia patients use cannabis as a way to alleviate negative symptomatology including amotivation and use of the substance may indeed increase motivation and activation of brain reward circuitry. However prognosis and functional outcome of patient cannabis-users is thought to be worse than their non-using counterparts.

1.7. Rationale and Hypotheses

Some research has found increased MID reward sensitivity among chronic users of cannabis. Studies also report reduced reward sensitivity in unmedicated schizophrenia patients or those treated with typical antipsychotics. This effect has however been found to dissipate in schizophrenia patients treated with atypical antipsychotics. However, to knowledge, no study has investigated the behavioural and neural effects of chronic cannabis consumption on reward anticipation in schizophrenia. Due to the lack of control for cannabis

consumption history in MID studies in schizophrenia, it can be expected that a lack of group differences between healthy controls and schizophrenia patients treated with atypical antipsychotics could be the result of a hyposensitivity in non-using patients and hypersensitivity in patients with a history of cannabis use.

Using a MID paradigm, the current research aimed to investigate the motivational differences reflected in reward and punishment anticipation processing, as measured by the behavioural (accuracy and RT) and neural (BOLD) response to rewarding and punishing cues amongst four groups: (1) non-cannabis users with no psychiatric diagnosis, (2) cannabis-users with no psychiatric diagnosis, (3) schizophrenia patients with no history of cannabis use, (4) schizophrenia patients with a comorbid history of cannabis use. Based on the current state of knowledge the following hypotheses were made:

1) Control chronic cannabis users will display increased behavioural and neural sensitivity to reward anticipation in comparison to control non-users.
2) Schizophrenia patients will display no reward-related differences in behavioural or neural reward anticipation in comparison to healthy controls when considered as a homogenous group.
3) The net null effect of schizophrenia on reward anticipation sensitivity would be further explained by the additive effects of reward and punishment anticipation hyposensitivity in schizophrenia patient non-users and hypersensitivity in schizophrenia patient cannabis-users.

CHAPTER 2

2. Methodology

2.1 Participants: Schizophrenia

Data was collected from 89 participants. 40 of these were patients recruited from the psychosis unit of the Psychiatry Department of Eginition Hospital and were diagnosed by trained psychiatrists using criteria of the International Classification of Disorders ((ICD-10) (World Health Organization, 1992)). One patient received a diagnosis of psychosis not otherwise specified (F29), thirty-four were diagnosed with schizophrenia (F20) and five with brief psychotic disorder (F23), who were later diagnosed with schizophrenia at follow-up.

All patients were receiving antipsychotic medication at the time of data collection. 38 patients were prescribed atypical neuroleptics (risperidone, paliperidone, olanzapine, amisulpride, quetiapine, aripiprazole, clozapine) and two were receiving typical neuroleptics (haloperidole, trifluoperazine). No patient received benzodiazepines or beta-blockers on the day the study was carried out. At the time of testing, all patients were in a stable phase of disorder (they were not currently experiencing a psychotic episode and positive symptoms were in remission). The remaining 49 participants were healthy controls.

2.2 Participants: cannabis use

Patients and healthy controls were further subdivided into chronic cannabis-users and non-users, resulting in a total of four experimental groups. Cannabis users were required to have used the substance a minimum of once per week for one year, within the past year and non-users to have used cannabis a maximum of 15 times in their life. 16 patients were classified as cannabis users (SZ+C) and 24 as non-users (SZ-C). 22 healthy control participants were defined as users (HC+C) and 27 as non-users (HC-C), resulting in a total of 38 cannabis users (SZ+C and HC+C) and 51 non-users (SZ-C and HC-C). All cannabis-users were asked to abstain from using the drug for 24 hours prior to study completion to reduce

the likelihood of confounding subacute effects. Days since last use was recorded on the day the experiment was carried out.

Cannabis use data was collected from all participants included in the study. Collected information included age of first use, duration of use, frequency of use, type of cannabis used and other substance use. This data is presented in table 1. No included participants had a habitual history of other illicit substances besides cannabis. Type of cannabis used is not reported due to the majority of participants consuming multiple cannabis strains. There were no differences between HC+C and SZ+C in age of first use or duration of first use, nor were there differences between frequency of use nor lifetime usage.

Table 1: Group cannabis use data

	HC-C (n=27)	**HC+C (n=22)**	**SZ-C (n=21)**	**SZ+C (n=13)**	**p**
Age of first use (years)		16.91 *(2.09)*		15.46 *(2.22)*	0.06[a]
Duration of use (years)		7.78 *(5.42)*		6.67 *(4.16)*	0.54[a]
Frequency of use (times per week)		6.45 *(4.16)*		8.58 *(8.44)*	0.33[a]
Lifetime usage (number of times)	3.2 *(5.4)*	3443.8 *(4949)*	0.8 *(1.2)*	3488.3 *(4896)*	0.98[b]

Cannabis use data for the 83 participants that were included in the behavioural analysis: HC-C=non-cannabis user healthy controls, HC+C = cannabis-user healthy controls, SZ-C = non-cannabis user schizophrenia patients, SZ+C = cannabis-user schizophrenia patients. Age, duration and frequency of first use for HC-C and SZ-C were not reported since the majority had never used cannabis. Lifetime use is an estimation based on duration and frequency of use. All measures are equivalent to mean of respective group. Parentheses indicate standard deviation. p values for all variables indicate significance for testing differences between HC+C and SZ+C.

[a] independent samples t-test was used

[b] analysis of variance (ANOVA) was used.

2.3 Demographic data and laterality

Demographic measures included items concerning age, medication dosage, number of hospitalisations, disease onset date, education level, obstetric complications and urbanicity.

Dominant laterality was accounted for using a measure developed by Coren et al., (1979). The questionnaire consists of thirteen items measuring the dominant hand, foot, eye and ear of the participant.

2.4 Exclusion criteria and ethics

Patients (SZ+C and SZ-C) were excluded if they had been diagnosed with any neurological, neurodevelopmental or other psychiatric disorder, or if they had a habitual history of any illicit drug use other than cannabis.

Exclusion criteria for healthy controls (HC+C and HC-C) was current use of prescription medication or illicit substances other than cannabis, as well as a personal or familial history of psychiatric or neurological disorder.

Cannabis users (HC+C and SZ+C) were excluded if they had consumed cannabis within the past 24 hours.

All participants were presented with a detailed description of the study to ensure they fully understood the procedure and written informed consent was obtained before the study began. The protocol was approved by the ethics committee of Eginition Hospital and was conducted in accordance with the Declaration of Helsinki.

2.5 Monetary Choice Questionnaire

2.5.1 Background

The Monetary Choice Questionnaire (MCQ), developed by Kirby et al., (1999) is a self-report measure of delay discounting. This term describes the decrease in value of a future reward with the lengthening delay to that reward. An incentive that is further away is of lower present value. For this reason the likelihood of it being chosen over an alternative reward that will be received sooner, is lower. The rate at which a future reward reduces in present value increases with the length of delay and is known as the discount rate. Kirby (1997) noted that people's individual discount rates are variable.

Individuals who choose a smaller reward which occurs sooner over a larger reward which they must wait for are regarded as more impulsive. When both rewards are sufficiently delayed, preference reversals may occur which are illustrated in figure 1. At the point of presentation, both rewards have a similar value with a trivial preference for the larger, more delayed reward. At time point A, the present value of both rewards equalise, after which the value of the smaller reward increases at a steeper rate than the larger one. This is known as the window of vulnerability where choosing the smaller reward will result in an impulsive choice. The variability of this window is dependent on an individual's discount rate and the differences in value between the available rewards. Delay discounting involves a hyperbolic function whereby the present value is dependent on the reward amount, the delay time and the discount rate of the individual, known as the *k* value. *k* can be thought of as a measure of impulsivity whereby a higher *k* value indicates increased impulsiveness (Herrnstein, 1981).

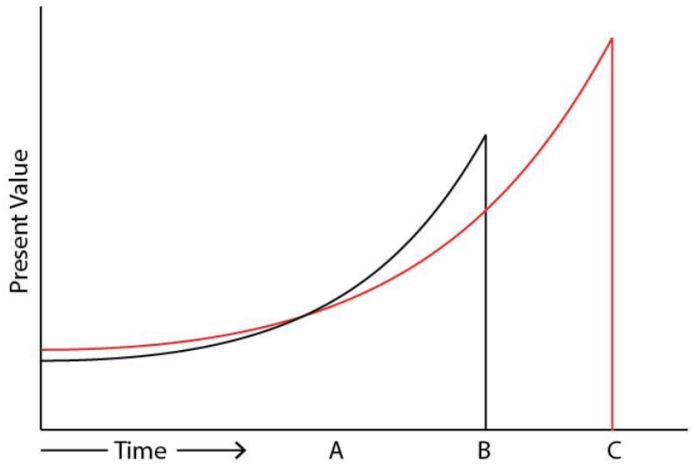
The MCQ has been implemented in many groups of people, including those addicted to alcohol (MacKillop et al., 2010), nicotine (Amlung & MacKillop, 2014), cocaine (Albein-Urios et al., 2014), and gambling (Gray & MacKillop et al., 2014) with varying results. In

cannabis users research has reported users to discount cannabis more steeply than money (Jarmolowicz et al., 2020) with a lack of differences in monetary discounting between users and non-users (Jarmolowicz et al., 2020; Gonzalez et al., 2012). Some studies have found trends towards steeper delay discounting in cannabis users compared to non-using controls, however it has been suggested that this effect size is smaller than for other substances (Johnson et al., 2010).

Schizophrenia patients have been found to more steeply discount future rewards than healthy controls (Heerey et al., 2007; Brown et al., 2018; Ahn et al., 2011) indicating higher levels of impulsivity. To our knowledge no study has investigated the results of the MCQ in both cannabis and schizophrenia.

The MCQ is a 27-item questionnaire with each item requiring the individual to choose between a smaller immediate reward (SIR) and a larger delayed reward (LDR). The items are divided into three magnitude groups: small, medium and large reward.

Figure 1: Present value of two delayed rewards



Reward delay illustration: Time point A demonstrates the point where both rewards hold equal value and preference switches from the larger reward to the smaller reward, B indicates a smaller, sooner reward, and C represents a later, larger reward. Adapted from Kirby et al., (1999).

2.5.2 Data acquisition

In the present study all monetary amounts were converted from United States Dollar (USD) to Euro (€) at the current conversion rate when the measure was implemented. A description of each item can be found in table 2 along with the proportion of participants in each group that selected the LDR. It can be seen that HC+C and SZ-C responded markedly more inconsistently than the other two groups. For each item a *k* indifference value is assigned, corresponding to the discount rate value where the SIR and LDR pose equal value. The indifference value was calculated using the equation from Mazur et al., (1987):

$$k = ((LDR/SIR)-1)/Delay$$

This measure was introduced after the initial commencement of data collection. MCQ data was gathered from 76 participants: 25 HC-C, 20 HC+C, 18 SZ-C and 13 SZ+C. That is, seven participants whose data is included in the behavioural sample are not included here: two HC-C, two HC+C and three SZ-C.

2.5.3 Analysis

Items were divided into small, medium and large reward for analysis purposes and within each category items were ordered from high to low *k* indifference value. For each participant, an individual discount rate was yielded for each category. If a participant chose the immediate reward in the small category for an item with indifference value of 0.0060 and the delayed reward on an item with an indifference value of 0.016 then this participant must have an individual discount rate of more than 0.0060 and less than 0.016. The geometric mean of these two values was then calculated to yield the *k* value for the small category for that participant. This technique may only be implemented when a participant made a clear switch at the point where they would choose the LDR to the point where they would choose the SIR. However responses are often inconsistent, particularly in the case of HC+C and SZ-

C as displayed in table 2. Ten bins were created, each representing a possible *k* value; eight bounded values as in the above example and two unbounded for each endpoint i.e. the most and least impulsive. A consistency value was calculated for each bin and the highest consistency value for that individual was taken to be their *k* value for that category. In the instance where two bins yielded the same consistency value, the geometric mean of the value of these bins was calculated to gain the discount rate. This procedure was repeated for each participant resulting in a discount *k* value for the small, medium and large reward categories.

Table 2: Monetary Choice Questionnaire item description

Reward values			**HC-C**			**HC+C**			**SZ-C**			**SZ+C**		
SIR	**LDR**	**Delay**	**S**	**M**	**L**	**S**	**M**	**L**	**S**	**M**	**L**	**S**	**M**	**L**
€30	€32	186	8			5			6			0		
€49	€50	117		4			10			**6**			0	
€70	€72	162			8			5			6			0
€25	€27	179	8			5			6			0		
€42	€45	160		4			5			**0**			0	
€73	€77	157			8			5			6			0
€20	€23	136	8			5			6			0		
€49	€54	111		4			5			**11**			8	
€60	€68	119			12			10			6			0
€23	€27	80	21			5			6			0		
€44	€54	89		24			10			**0**			8	
€63	€77	91			32			10			6			15
€17	€23	53	33			30			11			23		
€36	€50	62		52			**50**			**11**			38	
€50	€68	61			48			30			22			46
€22	€32	29	50			55			**28**			31		
€31	€45	30		56			**40**			17			38	
€49	€73	30			72			75			39			54
€13	€23	19	63			60			**22**			38		
€24	€45	21		72			80			56			54	
€37	€68	20			88			85			50			69
€14	€32	13	83			85			56			54		
€23	€54	14		84			85			72			69	
€30	€73	14			92			90			67			85
€10	€27	7	96			90			56			69		
€18	€50	7		96			100			78			92	
€28	€77	7			92			100			78			92

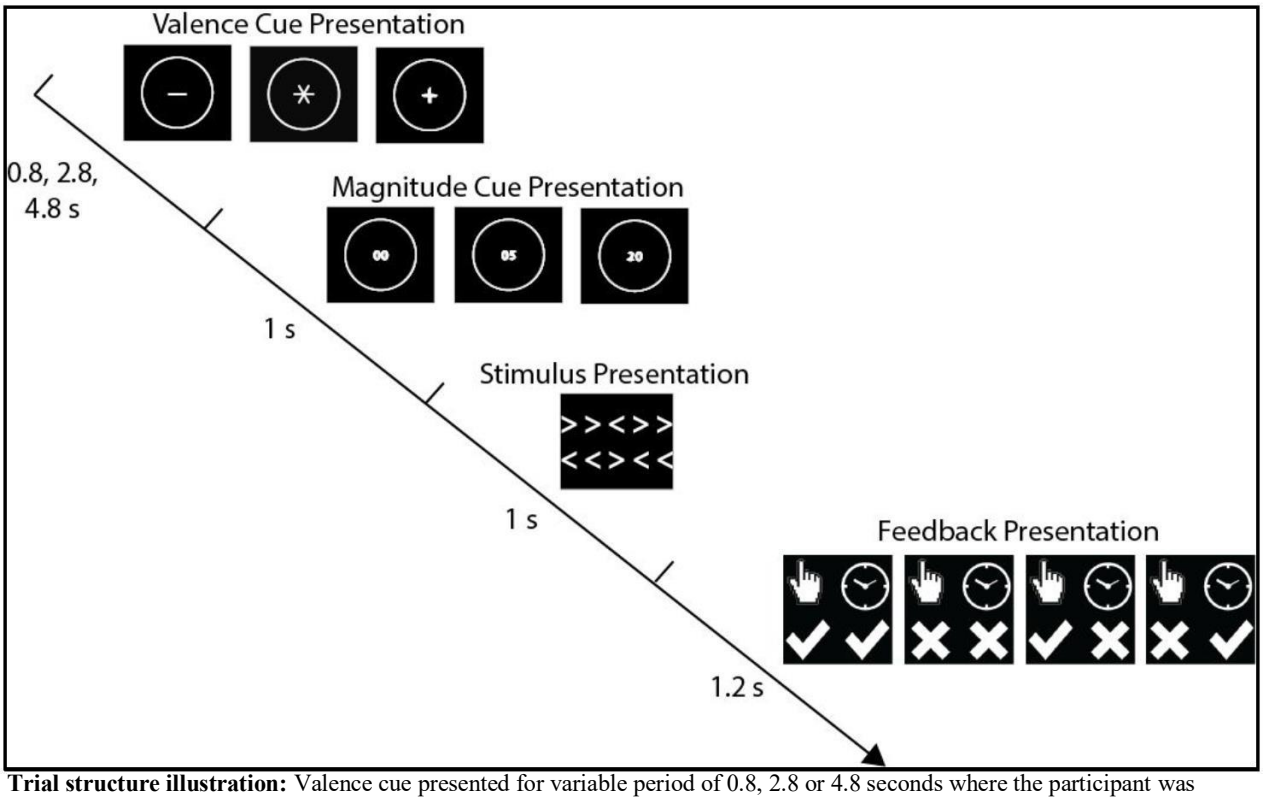
Item reward and delay information: Reward values displaying SIR: smaller immediate reward, LDR: larger delayed reward and delay period and proportion (%) of participants within each group electing the delayed reward on each item. HC-C = non-cannabis using healthy controls, HC+C = cannabis-using healthy controls, SZ-C = non-cannabis using schizophrenia patients, SZ+C = cannabis-using schizophrenia patients, S = small reward, M = medium delay, L = large delay. Bold typeface indicates group inconsistencies.

The distribution of discount rates were approximately normalised using natural log transformation as per Kirby et al., (1999). A 2x2x3 repeated measures analysis of variance (ANOVA) was carried out with cannabis (cannabis users and non-users) and schizophrenia (patients and healthy controls) as between-subjects factors and reward magnitude (small, medium and large) as the within-subjects factor.

2.6 Stimuli and procedure

The structure of the task is presented in figure 2. A two-choice RT task was used with elements of the MID and Eriksen flanker tasks. The participant held a response pad (Cedrus, California, USA) and was instructed to respond to a series of five arrow heads appearing for a fixed period, with their right or left index finger, in accordance with the pointing direction of the central arrowhead. Only the incongruent configuration of the arrow heads was used (< < > < < or > > < > >). Preceding the stimulus, a valence cue was first presented, for a variable period (0.8, 2.8 or 4.8 seconds), consisting of either + (win), - (lose) or *(neutral), followed by the magnitude cue representing the amount of the upcoming potential reward or punishment (high: 20, low: 5, or none: 0) that was presented for one second. After the one second response period, feedback was presented for 1.2 seconds. The participant was informed that the aim of the task was to gain a maximal amount of points and in order for them to win (+) or avoid losing (–), they must respond both accurately and quickly. The task was divided into six blocks of sixty trials with the first block consisting solely of neutral trials, used to generate a baseline mean RT from each participant's correctly answered trials. On subsequent blocks, the participant completed a trial successfully if they responded with the correct button press and faster or equal to their mean RT from the first block. These five blocks each contained twelve trials of each condition (high punishment, low punishment, neutral, low reward, high reward). At the end of the task, the participant was informed of their final score, 1500 being the maximum.

Figure 2: Trial structure illustration



Trial structure illustration: Valence cue presented for variable period of 0.8, 2.8 or 4.8 seconds where the participant was informed if the current trial could lead to a potential punishment (-), neutral trial (*), or could lead to a potential win (+), followed by the magnitude cue presented for a fixed period of one second where the participant was presented with the number of points at stake for the current trial: 00 (neutral trials only), 05 (low reward and punishment), or 20 (high reward and punishment). During presentation of the stimulus for a fixed one second period the participant was required to respond both accurately (left or right button press in accordance with the pointing direction of the central arrowhead) and quickly (faster or equal to their mean reaction time (RT) from the first block). The participant was finally presented with a feedback screen for 1.2 seconds, presenting the outcome of the response for the current trial and informing the participant if they had completed the trial successfully.

2.7 Behavioural data acquisition and analysis

Accuracy and RT data were analysed for the five blocks of the MID task. Six patients (3 SZ-C, 3 SZ+C) were excluded from the behavioural analysis due to a <70% accuracy rate, resulting in a total of 83 included participants. Accuracy and RT were recorded for each participant and each condition. RTs <120ms were excluded, considered as anticipatory responses. Total mean accuracy and RT were calculated for each condition.

A global analysis was performed for accuracy and mean RT using the general linear model (GLM) and a 2x2x5 analysis of covariance (ANCOVA) design. Reward/punishment condition was the within-subject repeated measures factor (5 levels) while cannabis use and

schizophrenia were between-group fixed factors (2 levels each). Due to the fact that years of education was significantly different between groups, and age was approaching significance, these demographic variables were included as continuous covariates in all between-subjects analyses. Since the focus of this study was the interaction of reward and punishment effects with cannabis use and schizophrenia we report only the reward and punishment related effects of this analysis and not the main effects of cannabis, schizophrenia and their interaction.

A second analysis was performed to investigate the nature of the significant interaction effects between conditions and group factors. Following the same rationale as will be presented subsequently for the analysis of the imaging data, three specific contrast values were computed for accuracy and three for mean RT, for each subject as follows:

- valence: difference between the neutral condition and the mean of all valence conditions
- reward versus punishment: difference between mean of reward and mean of punishment conditions.
- magnitude: difference between the mean of low magnitude plus neutral conditions and the mean of high magnitude conditions.

Figure 3 demonstrates which conditions were included in each contrast. These contrast values for each subject were used as dependent variables in a GLM 2x2 ANCOVA with cannabis use and schizophrenia as fixed factors and years of education and age as continuous covariates.

The GLM tool in Statistica 12 (StatSoft Inc., 1984-2014) was used for all analyses of behavioural data.

Figure 3: Illustration of contrasts

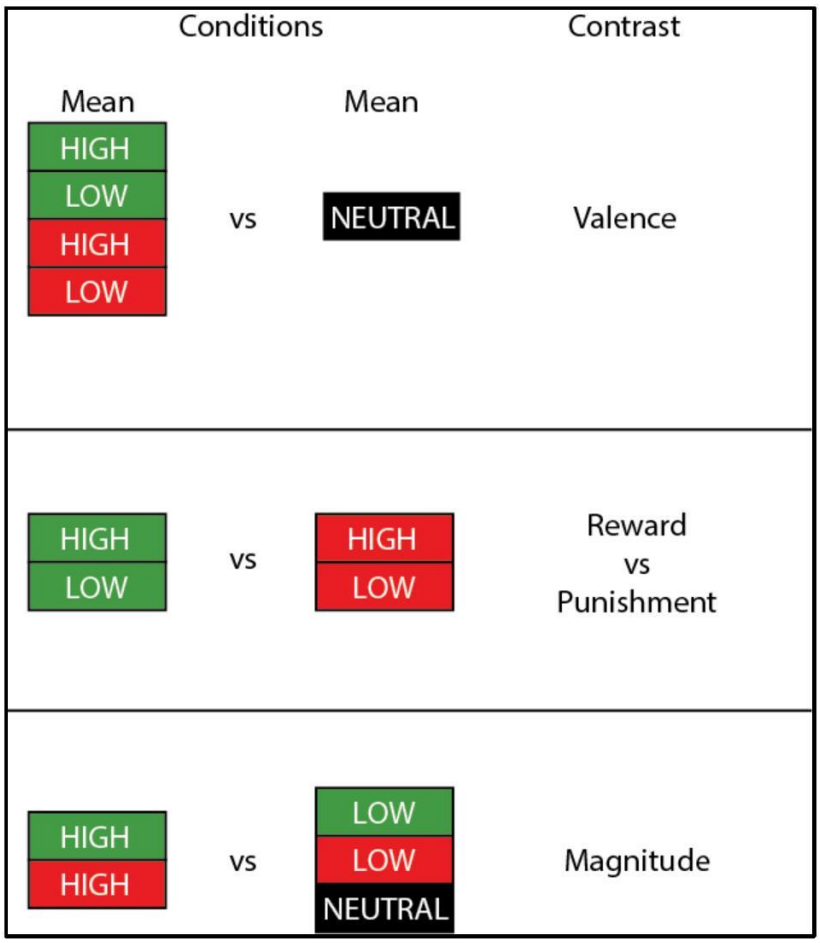


Illustration of contrasts: Green = reward, red = punishment, black = neutral. Valence contrast= mean of high reward + low reward + high punishment + low punishment versus neutral. Reward versus punishment contrast = mean of high reward + low reward versus mean of high punishment + low punishment. Magnitude contrast = mean of high reward + high punishment versus mean of low reward + low punishment + neutral.

2.8 Imaging methodology

2.8.1 fMRI data acquisition and pre-processing

Functional magnetic resonance (MR) images were acquired using a Philips Achieva 3.0 Tesla TX MRI scanner using echo-planar imaging with 2 second repetition time (TR), 36 slices and 3x3x3mm voxel size. A high resolution T1 anatomical image with 1x1x1mm voxel size was also acquired for each participant. Quality control was performed using ArtRepair software (Center for Interdisciplinary Brain Sciences, Stanford University, USA). Ten

participants (1 HC-C, 4 HC+C, 4 SZ-C, 1 SZ+C) were excluded due to low image quality, resulting in a sample of 73 participants.

SPM12 toolbox for MATLAB (Wellcome Trust Centre for Neuroimaging, London, UK) was used for all imaging data analysis. Pre-processing was first performed by spatially realigning the raw images and temporal interpolation was completed to correct for delay in slice acquisition. Data with registered motion >3 mm or 1 degree was excluded. The T1 image was next used to segment the images into grey and white matter and cerebrospinal fluid (CSF). Images were normalized to standard Montreal Neurological Institute (MNI) space and smoothed with an 8mm full width at half maximum (FWHM) Gaussian kernel. A high-pass filter of 128s cut off was applied, to eliminate physiological components such as respiration or heartbeat.

2.8.2 First-level analysis

Onset times for each condition were extracted for both valence and magnitude cues, with the relative duration for each specific trial and cue type. A first-level within-subject analysis was carried out for both valence and magnitude separately, whereby a GLM was applied to the images from each participant. Three regressors, reward (+), punishment (-) and neutral (*) were included for the valence model. Five regressors (-20, -5, 0, +5, +20) were included for the magnitude model. Additional regressors included motion correction parameters estimated from the realignment step of the pre-processing. T-contrasts were calculated to measure the contrasts of valence, reward/punishment and magnitude and were defined as previously described. The valence and reward/punishment contrasts were calculated in the valence model while all three contrasts were calculated in the magnitude model.

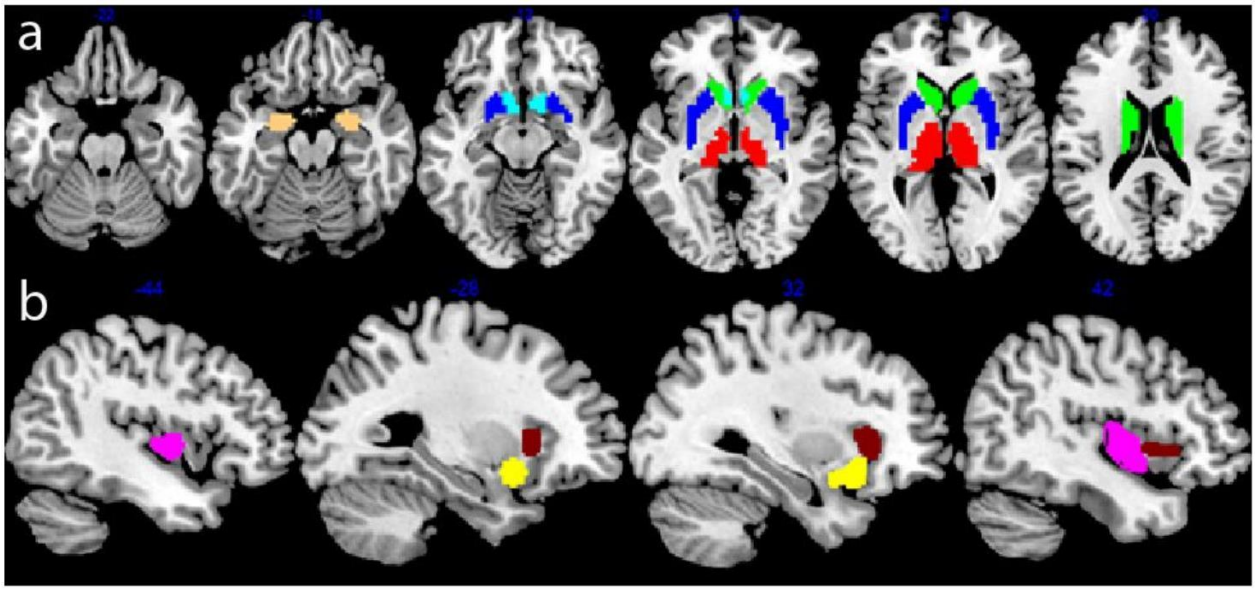
2.8.3 Second-level: validation analysis

At the second-level, a validation region of interest (ROI) analysis was first carried out to verify that reward and punishment-related regions were activated during the two cue periods. One-sample t-tests were carried out for each contrast. The following ROIs were selected and included in the present study based on a recent meta-analysis of neural activation in the MID task, reporting activation in common regions for reward and punishment anticipation; striatum, thalamus, amygdala and insula (Oldham et al., 2018). Striatum was divided into subcomponents of NAcc, caudate and putamen and were defined structurally along with thalamus and amygdala, using the AAL3 atlas. Considering the anatomically and functionally distinct insular sub-regions (Deen et al., 2011) and their involvement in reward tasks (Yoon et al., 2015; Kirk et al., 2015), insula was divided into sub-regions of dorsal and ventral anterior, as well as posterior. Using mean MNI coordinates from a prior study (Deen et al., 2011), the insular sub-regions were manually defined on T1 (Moran et al., 2013) in order to ensure the inclusion of all anatomically relevant regions and the exclusion of anatomically irrelevant regions. All ROIs were defined in MNI space for both right and left hemispheres. Final ROIs are presented in figure 4. Activation within each ROI was assessed with an inclusive mask. A small-volume corrected family-wise error (FWE) cluster-level threshold at $p<0.05$ in spheres of 10mm around ROI coordinates was used. A minimum cluster size threshold of three contiguous voxels was considered in all analyses to avoid type-one errors (Forman et al., 1995).

2.8.4 Second-level: main analysis

The main analysis was a 2x2 ANCOVA to assess the modulation of each contrast with cannabis use, schizophrenia status and their interaction, with years of education and age as covariates. Using Marsbar, beta values for each significant voxel cluster were extracted for each participant to assess the nature of the interaction by means of plots.

Figure 4: Regions of interest (ROI)



Regions of interest (ROI) included in all analyses: (a) peach = amygdala, blue = putamen, cyan = nucleus accumbens, red = thalamus, green = caudate. (b) violet = posterior insula, yellow = ventral anterior insula, brown = dorsal anterior insula.

CHAPTER 3

3. Results

3.1 Demographic and laterality results

Table 3 presents the results of the demographic and laterality data. There were no significant group differences in age, sex, medication, number of hospitalisations, duration of disorder, obstetric complications, urbanicity nor laterality. There was however a significant difference amongst the four groups in years of education with HC-C being enrolled in full time education for the most number of years and SZ-C for the least number of years ($F_{3, 79} = 12.41$, $p < 0.0001$, $\eta p^2 = 0.32$).

Table 3: Demographic and lateral dominance data

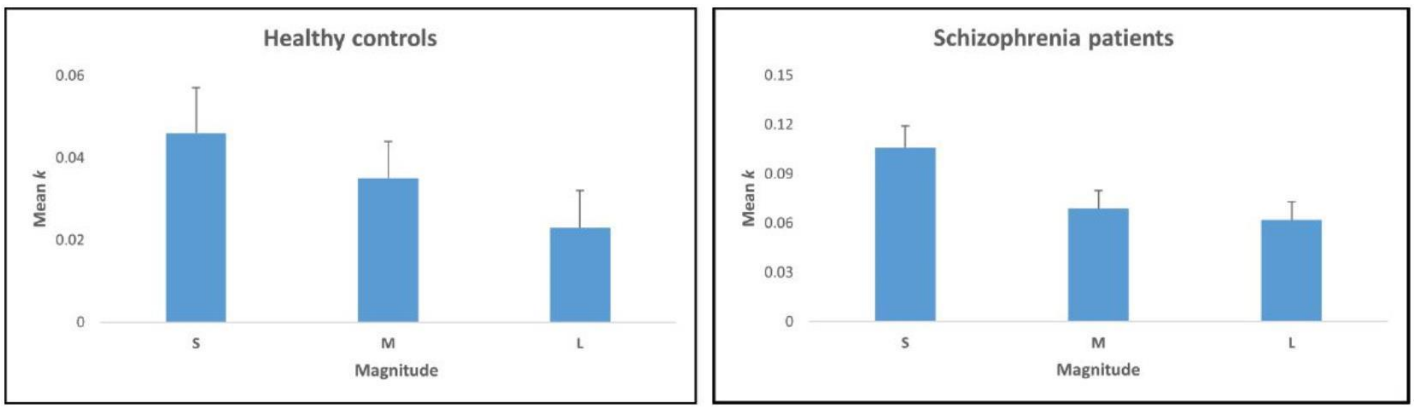
	HC-C	HC+C	SZ-C	SZ+C	p
Age (years)	27.82 (*4.63*)	27.05 (*7.72*)	30.29 (*8.00*)	23.92 (*4.75*)	0.056[a]
Sex (% male)	63	77	81	92	0.20[b]
Chlorpromazine equivalent (mg)			522 (*410*)	829 (*538*)	0.09[c]
Hospitalisations			1.44 (*0.94*)	1.09 (*0.54*)	0.32[c]
Disorder duration (years)			3.50 (*4.18*)	1.62 (*1.93*)	0.13[c]
Education (years)	15.63 (*0.79*)	14.64 (*1.68*)	12.76 (*1.86*)	13.46 (*1.66*)	**<0.0001[a]**
Obstetric complications (% reported)	0.00	0.00	4.76	15.38	0.056[b]
Urbanicity (% population > 80,000)	66.66	77.27	71.43	61.54	0.77[b]
Dominant laterality (% right)	81.49	81.82	95.24	84.62	0.50[b]

Demographic data for the 83 participants that were included in the behavioural analysis: HC-C=non-cannabis user healthy controls, HC+C = cannabis-user healthy controls, SZ-C = non-cannabis user schizophrenia patients, SZ+C = cannabis-user schizophrenia patients. Parentheses indicate standard error of mean.
[a] analysis of variance (ANOVA) was used
[b] chi-square test was used
[c] independent samples t-test was used. Bold typeface = $p<0.05$.

3.2 MCQ results

Descriptive statistics for each group and magnitude condition are displayed in table 4. There was a significant main effect of magnitude ($F_{2, 144} = 24.49$, $p < 0.001$, $\eta_p^2 = 0.25$). Bonferroni comparisons revealed that all participants were more impulsive on small magnitude items than medium or large magnitude items. There was no significant main effect of cannabis ($F_{1, 72} = 0.69$, $p = 0.41$, $\eta_p^2 = 0.01$), nor two-way interaction effect of cannabis*condition ($F_{2, 144} = 1.44$, $p = 0.24$, $\eta_p^2 = 0.02$). There was however a main effect of schizophrenia ($F_{1, 72} = 9.66$, $p = 0.003$, $\eta_p^2 = 0.12$) whereby patients were generally more impulsive than controls. There was also a significant two-way schizophrenia*condition interaction, ($F_{2, 144} = 3.98$, $p = 0.021$, $\eta_p^2 = 0.05$). Figure 5 demonstrates this interaction. Schizophrenia patients were more impulsive on small magnitude compared to medium and large magnitude items, whereas the impulsiveness of healthy controls decreased in a more linear fashion from small to medium to large magnitude. There was no significant three-way cannabis*schizophrenia*condition interaction ($F_{2, 144} = 1.48$, $p = 0.23$, $\eta_p^2 = 0.02$). Due to the lack of cannabis*schizophrenia interaction effects, this data is not included in any subsequent analyses.

Figure 5: Mean k values for patients and controls



Mean *k* values for each magnitude for healthy controls (HC-C and HC+C) (left) and schizophrenia patients (SZ-C and SZ+C) (right). Error bars indicate standard error of the mean.

Table 4: Group mean discount value (*k*)

	HC-C	HC+C	SZ-C	SZ+C
S	0.046 (*0.02*)	0.046 (*0.02)*	0.115 (*0.02*)	0.100 (*0.02*)
M	0.038 (*0.01*)	0.032 (*0.01*)	0.074 (*0.01*)	0.066 (*0.02*)
L	0.025 (*0.01*)	0.022 (*0.01*)	0.083 (*0.01)*	0.043 (*0.02*)
Total	0.036 (*0.01*)	0.033 (*0.01*)	0.090 (*0.01*)	0.069 (*0.02*)

Mean *k* value for each group. S = small, M = medium, L = large, HC-C = healthy control non-cannabis users, HC+C = healthy control cannabis users, SZ-C = schizophrenia patient non-cannabis users, SZ+C = schizophrenia patient cannabis users. Parentheses indicate standard error of mean.

3.3 Behavioural results

3.3.1 Global analysis

Descriptive statistics for the global analysis are presented in table 5. There was no significant effect of condition on accuracy ($F_{4, 308} = 1.78$, $p = 0.132$, $\eta_p^2 = 0.022$). There was no significant interaction of condition x cannabis use ($F_{4, 308} = 1.54$, $p = 0.19$, $\eta_p^2 = 0.019$), no significant interaction of condition x schizophrenia ($F_{4, 308} = 1.6$, $p = 0.174$, $\eta_p^2 = 0.02$) and no significant three-way interaction of condition x cannabis x schizophrenia ($F_{4, 308} = 2.04$, $p = 0.088$, $\eta_p^2 = 0.026$) on accuracy.

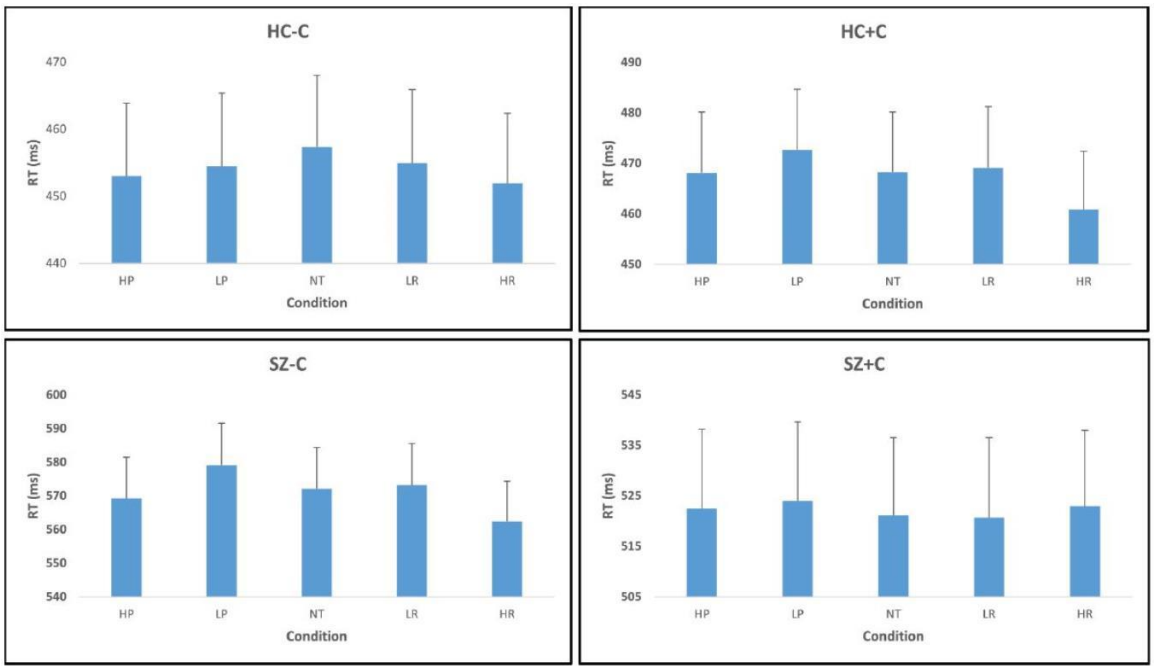
The effect of condition on RT was not significant ($F_{4, 308} = 0.86$, $p = 0.485$, $\eta_p^2 = 0.011$) and there was no significant interaction of condition x cannabis use ($F_{4, 308} = 0.66$, $p = 0.617$, $\eta_p^2 = 0.008$) nor condition x schizophrenia ($F_{4, 308} = 0.61$, $p = 0.659$, $\eta_p^2 = 0.008$). There was however a highly significant three-way interaction of condition x cannabis x schizophrenia ($F_{4, 308} = 3.05$, $p = 0.017$, $\eta_p^2 = 0.038$) on RT. The global analysis was also performed on the 73 individuals that were retained in the imaging analysis and the results were similar (not presented). Group RTs for each condition are presented in figure 6.

Table 5: Behavioural global analysis descriptive statistics

Measure	Accuracy (%)				RT (ms)			
	HC-C	**HC+C**	**SZ-C**	**SZ+C**	**HC-C**	**HC+C**	**SZ-C**	**SZ+C**
HP	96.9 *(0.01)*	96.7 *(0.01)*	93.6 *(0.01)*	95.8 *(0.01)*	452.98 *(10.90)*	468.08 *(12.07)*	569.18 *(12.36)*	522.50 *(15.71)*
LP	96.4 *(0.01)*	96.7 *(0.01)*	92.2 *(0.01)*	94.5 *(0.01)*	454.49 *(10.88)*	472.63 *(12.05)*	579.17 *(12.34)*	523.92 *(15.68)*
NT	96.5 *(0.01)*	96.0 *(0.01)*	92.1 *(0.01)*	91.9 *(0.01)*	457.34 *(10.72)*	468.30 *(11.88)*	572.15 *(12.16)*	521.07 *(15.45)*
LR	96.7 *(0.01)*	95.1 *(0.01)*	94.1 *(0.01)*	95.6 *(0.01)*	454.93 *(10.96)*	469.07 *(12.14)*	573.16 *(12.43)*	520.70 *(15.80)*
HR	96.2 *(0.01)*	95.5 *(0.01)*	93.2 *(0.01)*	94.1 *(0.02)*	451.91 *(10.47)*	460.80 *(11.59)*	562.42 *(11.87)*	522.94 *(15.08)*
Total	96.5 *(0.1)*	96.0 *(0.01)*	93.0 *(0.01)*	94.4 *(0.1)*	454.33 *(10.60)*	467.78 *(11.74)*	571.21 *(12.02)*	522.23 *(15.28)*

Descriptive statistics for behavioural global analysis. HP = high punishment, LP = low punishment, NT = neutral, LR = low reward, HR = high reward, HC-C = healthy control non-users, HC+C = healthy control cannabis users, SZ-C = schizophrenia patient non-users, SZ+C = schizophrenia patient cannabis users. Accuracy = % correct responses, RT = Reaction time in ms between stimulus presentation and button-press. Values indicate mean for each group and condition. Parentheses indicate standard error of mean.

Figure 6: Group reaction times (RT)



Reaction times (RT) for each group and condition. HP = high punishment, LP = low punishment, NT = neutral, LR = low reward, HR = high reward, HC-C = healthy control non-users, HC+C = healthy control cannabis users, SZ-C = schizophrenia patient non-users, SZ+C = schizophrenia patient cannabis users. Error bars indicate standard error of mean. RT is displayed in milliseconds.

3.3.2 Contrast analysis

Descriptive statistics for the contrast analysis are presented in table 6. Results from the global analysis revealed significant interactions for RT only. Thus, only this measure was further investigated in the contrast analysis. The valence contrast was not modulated by cannabis use ($F_{1, 77} = 1.23$, $p = 0.27$, $\eta_p^2 = 0.016$), neither by schizophrenia ($F_{1, 77} = 0.19$, $p = 0.66$, $\eta_p^2 = 0.002$), nor their interaction ($F_{1, 77} = 0.53$, $p = 0.47$, $\eta_p^2 = 0.007$). The reward versus punishment contrast was not modulated by cannabis use ($F_{1, 77} = 0.002$, $p = 0.97$, $\eta_p^2 = 0.0002$) nor by schizophrenia ($F_{1, 77} = 1.4$, $p = 0.24$, $\eta_p^2 = 0.018$) but was significantly modulated by their interaction ($F_{1, 77} = 4.57$, $p = 0.036$, $\eta_p^2 = 0.056$) (figure 7a). This effect was however not retained when using the 73 individuals of the imaging sample ($F_{1, 67}$=2.98, p = 0.088, ηp2 = 0.042).

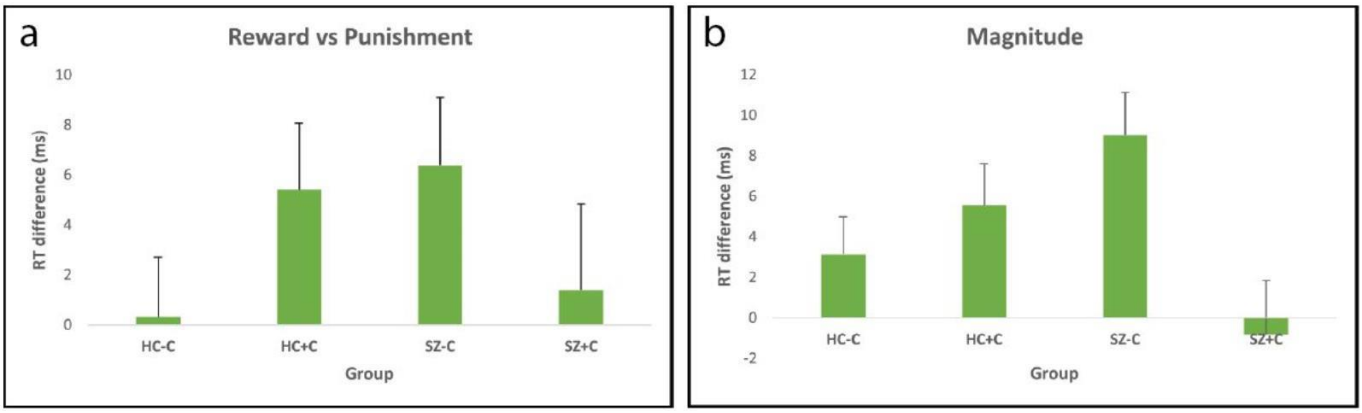
Finally the magnitude contrast was not significantly modulated by cannabis use ($F_{1, 77} = 2.74$, $p = 0.10$, $\eta_p^2 = 0.033$) nor schizophrenia ($F_{1, 77} = 0.27$, $p = 0.60$, $\eta_p^2 = 0.003$) but was significantly modulated by their interaction ($F_{1, 77} = 7.64$, $p = 0.007$, $\eta_p^2 = 0.09$).This effect was also retained when using the 73 individuals of the imaging sample ($F_{1, 67} = 8.86$, $p = 0.004$, $\eta_p^2 = 0.117$). Figure 7b demonstrates that the magnitude contrast in RT (corresponding to an increase in speed for the high reward and punishment magnitude cues compared to low magnitude and neutral cues) was larger in HC+C compared to HC-C, while the opposite effect was observed for schizophrenia patients, namely a decrease for SZ+C compared to SZ-C.

Table 6: Behavioural contrast analysis descriptive statistics

Contrast	Group			
	HC-C	**HC+C**	**SZ-C**	**SZ+C**
Valence	3.77 *(3.04)*	0.66 *(3.36)*	1.17 *(3.44)*	-1.45 *(4.37)*
Rew vs pun	0.32 *(2.39)*	5.42 *(2.65)*	6.38 *(2.71)*	1.39 *(3.44)*
Magnitude	3.15 *(1.84)*	5.56 *(2.04)*	9.02 *(2.09)*	-0.82 *(2.65)*

Descriptive statistics for contrast analysis. Values indicate mean reaction time (RT) difference (ms). Parentheses indicate standard error of the mean. HC-C = healthy control non-users, HC+C = healthy control cannabis users, SZ-C = schizophrenia patient non-users, SZ+C = schizophrenia patient cannabis users. Valence = (neutral) minus (high punishment + low punishment + low reward + high reward), Rew vs pun = (high punishment + low punishment) minus (low reward + high reward), Magnitude = (low punishment + neutral + low reward) minus (high punishment + high reward).

Figure 7: Between-group reaction time (RT) differences



Reaction time (RT) differences between groups: Mean RT difference (ms) for each group. ms = milliseconds, HC-C = non-cannabis user healthy controls, HC+C = cannabis-user healthy controls, SZ-C = non-cannabis user schizophrenia patients, SZ+C = cannabis-user schizophrenia patients. Error bars indicate standard errors of the mean differences. (a) demonstrates the reward versus punishment contrast, (b) demonstrates the magnitude contrast.

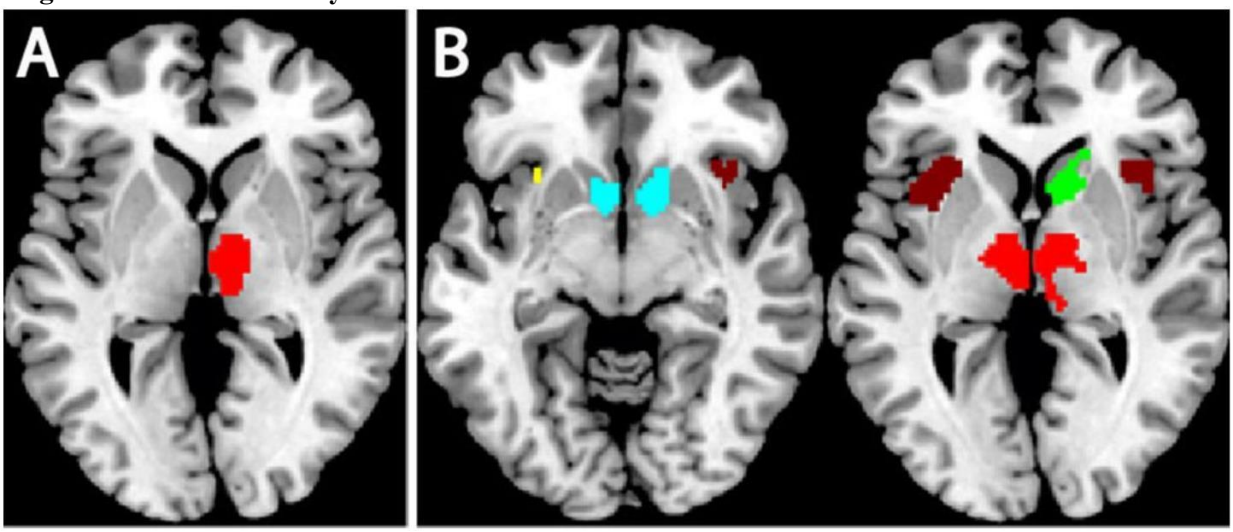
3.4 Imaging Results

3.4.1 Validation analysis

Table 7 presents the results of the validation analysis. One-sample t-tests across all subjects confirmed that reward and punishment-related regions, assessed by ROI analysis, were more highly activated in both the valence and magnitude models. The valence contrast yielded higher right thalamic activation for incentive conditions compared to neutral during

the valence cue period (figure 8a). Additional regions were significantly more highly activated for the valence contrast during presentation of the magnitude cue including the left thalamus and left ventral anterior insula as well as bilateral dorsal anterior insula, bilateral NAcc, and right caudate (figure 8b). The magnitude contrast revealed high magnitude compared to low magnitude plus neutral cues further activated the right ventral anterior insula and right amygdala (figure 9) as well as the left caudate. There were no differences in activation when comparing reward and punishment conditions in any pre-defined ROI.

Figure 8: Validation analysis results: valence contrast



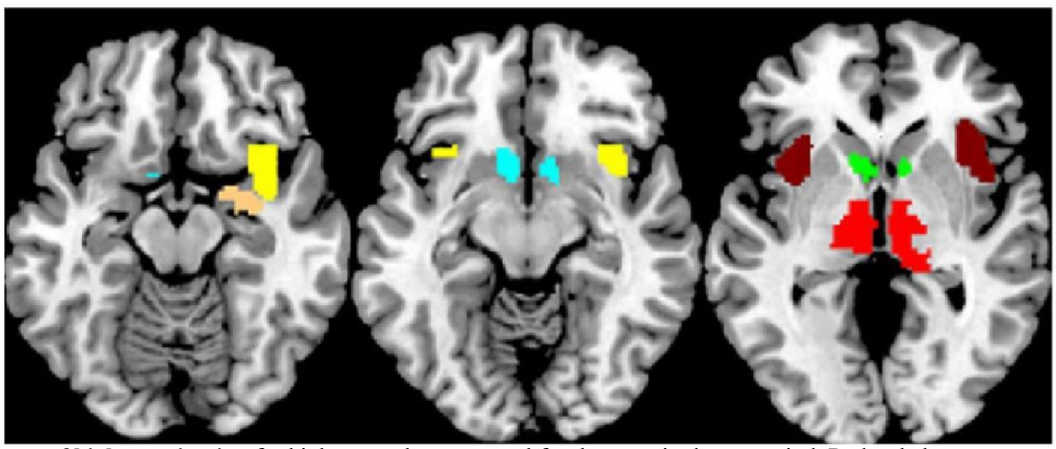
Validation analysis. Clusters of higher activation for valence contrast for the valence (a) and magnitude (b) cue period. Red = thalamus; green = caudate; cyan = nucleus accumbens; brown = dorsal anterior insula; yellow = ventral anterior insula.

Table 7: Results of regions of interest (ROI) validation analysis

Contrast	Anatomical labelling		Statistics			MNI coordinates		
	Label	Hemisphere	Z	p(svc)	K_E	x	y	z
Reward + Punishment > Neutral								
Valence model	Thalamus	R	3.84	0.003	20	9	-7	-2
Magnitude model	dAI	L	4.24	0.001	38	-33	23	-2
		R	3.39	0.013	17	42	17	-2
	vAI	L	3.65	0.006	3	-30	20	-5
	NAcc	L	3.33	0.015	5	-3	8	-5
		R	4.60	0.000	25	9	5	-5
	Caudate	R	4.42	0.000	16	9	5	-2
		R	3.28	0.017	3	18	26	1
	Thalamus	L	3.73	0.004	27	-6	-10	-2
		R	3.79	0.003	31	3	-10	1
Reward > Punishment								
Valence model	-	-	-	-	-	-	-	-
Magnitude model	-	-	-	-	-	-	-	-
High > Low + Neutral								
Magnitude model	Caudate	L	4.36	0.000	17	-6	8	-2
		R	4.11	0.001	14	9	5	-2
	NAcc	L	4.26	0.001	29	-6	8	-5
		R	4.38	0.000	12	9	5	-5
	Amygdala	R	4.18	0.001	12	18	-1	-17
	Thalamus	L	3.82	0.003	62	-15	-10	10
		R	3.94	0.002	39	6	-4	4
	dAI	L	3.87	0.002	23	-33	23	-5
		R	4.57	0.000	43	33	23	-8
	vAI	L	3.78	0.003	15	-36	17	-5
		R	4.71	0.000	35	30	20	-11

Region of interest (ROI) validation analysis for the three contrasts using the valence and magnitude cue models. MNI = Montreal Neurological Institute; svc = small volume correction; R = right; L = left; K_E = number of voxels in cluster; dAI = dorsal anterior insula; vAI = ventral anterior insula; NAcc = nucleus accumbens. We applied family-wise error (FWE) correction adjusted for small-volume [p (svc) < 0.05] within each of the independent ROIs at the voxel level (only ROIs with at least 3 contiguous voxels were considered significant). There were no significantly different regions for the reward vs punishment contrast.

Figure 9: Validation analysis results: magnitude contrast



Clusters of higher activation for high versus low + neutral for the magnitude cue period. Red = thalamus; green = caudate; cyan = nucleus accumbens; peach = amygdala; brown = dorsal anterior insula; yellow = ventral anterior insula.

3.4.2 Main analysis

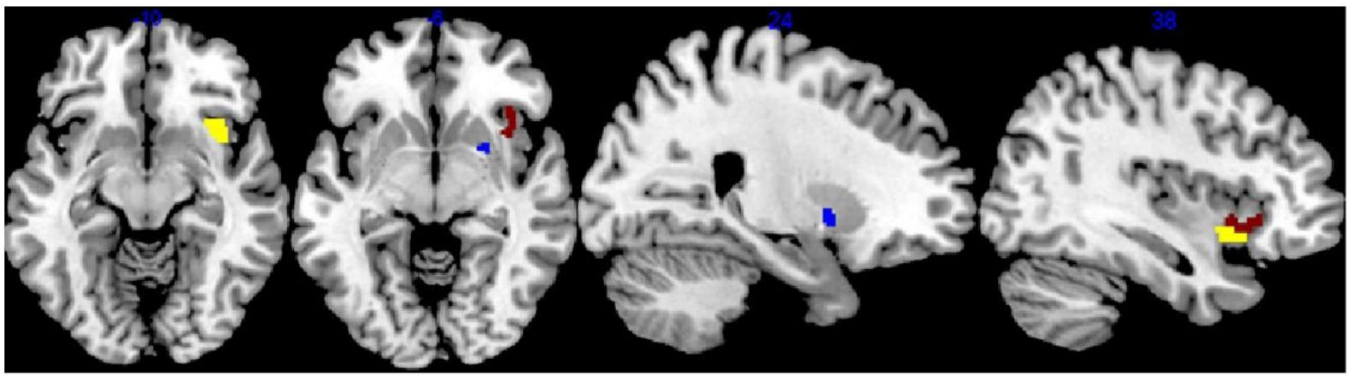
Based on the results of the validation analysis, the main analysis was carried out on the contrasts for the magnitude model. Between-subjects results of the main analysis including the effects of cannabis, schizophrenia and their interaction are presented in table 8. There were no between-group differences, nor interaction effects for the valence contrast. A main effect of cannabis use and an interaction of cannabis use and schizophrenia was observed for the reward versus punishment contrast. Extraction of beta values showed an increased activation in the right putamen, right dorsal anterior insula and right ventral anterior insula for reward versus punishment for cannabis users (HC+C and SZ+C) compared to non-users (HC-C and SZ-C) (figure 10). Activation in the right thalamus was also larger for reward versus punishment for the HC+C and SZ-C groups versus HC-C and SZ+C groups (figure 11a). For the magnitude contrast, there was no main effect of cannabis nor schizophrenia while an interaction of these two factors appeared for left ventral anterior insula, left dorsal anterior insula and bilateral posterior insula. Following beta value extraction it was shown that HC+C exhibited increased activation in each of the above-mentioned regions compared to HC-C, while the opposite pattern was observed for patients, namely SZ+C displayed activation decreases in all these regions compared to SZ-C (figure 11b).

Table 8: Results of regions of interest (ROI) main analysis

Contrast	Anatomical labelling		Statistics			MNI coordinates		
	Label	Hemisphere	F	p(svc)	K_E	x	y	z
Reward + Punishment > Neutral								
Cannabis	-	-	-	-	-	-	-	-
Diagnosis	-	-	-	-	-	-	-	-
Interaction	-	-	-	-	-	-	-	-
Reward > Punishment								
Cannabis	Putamen	R	15.89	0.009	4	24	5	-2
	vAI	R	14.09	0.017	8	39	14	-8
	dAI	R	14.42	0.015	6	39	17	-8
Diagnosis	-	-	-	-	-	-	-	-
Interaction	Thalamus	R	14.48	0.015	5	3	-19	7
High > Low + Neutral								
Cannabis	-	-	-	-	-	-	-	-
Diagnosis	-	-	-	-	-	-	-	-
Interaction	vAI	L	15.93	0.008	12	-39	-1	-5
	dAI	L	14.46	0.014	3	-39	2	-2
	pI	R	22.81	0.001	19	42	-10	13
		L	16.05	0.008	16	-42	2	-8

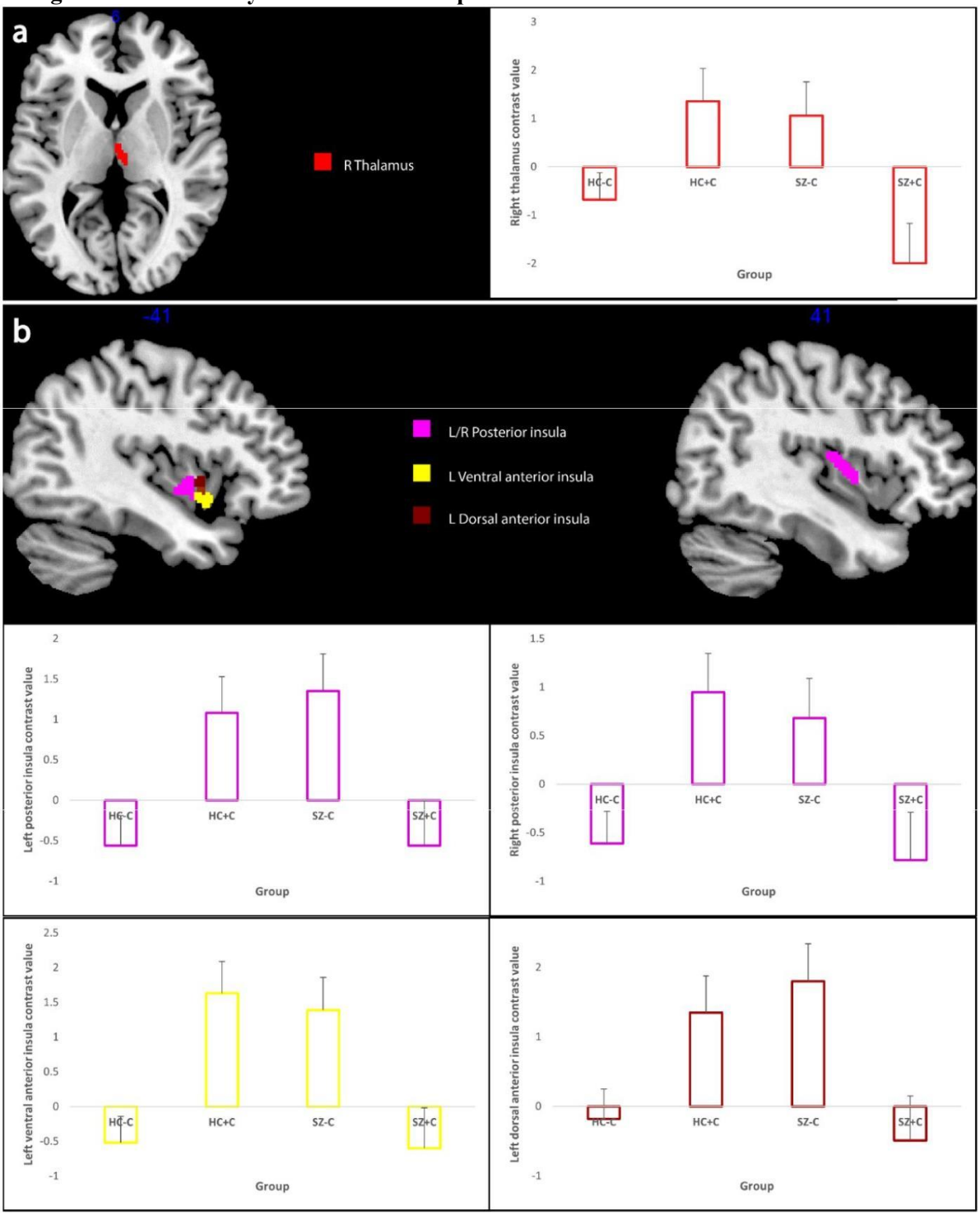
Region of interest (ROI) main analysis displaying the effects of cannabis and schizophrenia on each contrast of interest as well as the cannabis by schizophrenia interactions. MNI = Montreal Neurological Institute; svc = small volume correction; R = right; L = left; vAI = ventral anterior insula; dAI = dorsal anterior insula; pI = posterior insula. We applied family-wise error (FWE) correction adjusted for small-volume [p (svc) < 0.05] within each of the independent ROIs at the voxel level (only ROIs with at least 3 contiguous voxels were considered significant).

Figure 10: Main analysis cannabis effect results: reward versus punishment



Clusters of higher activation for cannabis users compared to non-users for the reward vs punishment contrast. Yellow = ventral anterior insula; brown = dorsal anterior insula; blue = putamen.

Figure 11: Main analysis cannabis*schizophrenia*reward results



Clusters showing significant modulation by the interaction of cannabis and schizophrenia for the reward versus punishment contrast (a) and the magnitude contrast (b). Clusters thresholded at $p < 0.005$ for visualisation purposes. Red = thalamus; yellow = ventral anterior insula; brown = dorsal anterior insula; violet = posterior insula. The bar plots show mean beta values for each cluster for each group and error bars show standard errors of the mean beta values. HC-C = non-cannabis user healthy controls, HC+C = cannabis-user healthy controls, SZ-C = non-cannabis user schizophrenia patients, SZ+C = cannabis-user schizophrenia patients.

CHAPTER 4

4. Discussion

The relationship between chronic cannabis consumption, schizophrenia and reward and punishment anticipation is of a complex nature with contradictory research demonstrating opposing effects of both factors on incentive processing. Similarly the relationship between cannabis and schizophrenia is complex and multifaceted with higher incidence of psychotic experience in healthy users of cannabis, higher incidence of cannabis use in schizophrenia patients as well as differences in the cognition, neurobiology and functional outcome between patient-users and patient non-users. The multitude of effects of history of cannabis use in schizophrenia patients is vast and not yet fully understood.

The current study aimed to address a gap in the research, investigating the interaction of chronic cannabis use and schizophrenia on behaviour and neural activation related to the anticipation of reward and punishment in a two-choice RT task in order to gain insight into the role that cannabis plays in the motivation of schizophrenia patients.

4.1 Delay discounting findings

Cannabis users did not differ from non-users on the MCQ, in line with previous findings (Jarmolowicz et al., 2020; Gonzalez et al., 2012) suggesting that this group only discount cannabis more steeply than monetary rewards. However, schizophrenia patients did display more impulsiveness than healthy controls, which is in line with previous findings (Heerey et al., 2007; Brown et al., 2018; Ahn et al., 2011). Additionally, schizophrenia patients displayed higher levels of impulsivity for smaller rewards in comparison to medium and larger rewards, whereas the impulsivity of healthy controls was more relative to the reward size. No interaction between cannabis use and schizophrenia was found on this measure, suggesting that any group differences in reward anticipation sensitivity are not directly related to level of impulsivity.

4.2 Reward and punishment-related effects of chronic cannabis use and schizophrenia on reaction time

There was no overall modulation of accuracy by reward and punishment and there was also no effect of cannabis nor schizophrenia nor their interaction on reward and punishment-related accuracy. This reflects the simplistic nature of the task and confirms its fit to the cognitive capacity of all groups.

There was also no overall modulation of RT by reward and punishment. While some previous studies have found incentive condition to modulate RT independent of group (Nestor et al., 2010; van Hell et al., 2010), others have not (Enzi et al., 2015). A significant main effect of condition on RT was found prior to the inclusion of covariates, however accounting for years of education as well as age resulted in no RT differences between conditions. This suggests the influence that the cue had on RT was small and therefore could not survive incorporation into a more powerful model.

There were no effects of cannabis use nor schizophrenia on reward and punishment-related RT. This is in accordance with previous research indicating no incentive-related RT differences between cannabis users (HC+C and SZ+C) and non-users (HC-C and SZ-C) (Nestor et al., 2010; van Hell et al., 2010).

While some studies have reported smaller RT differences between incentive and neutral trials in schizophrenia patients compared to controls (Stepien et al., 2018; Mucci et al., 2015), others, like the present study have reported no interactions of group and condition (Waltz et al., 2010; Kirschner et al., 2016; Schlagenhauf et al., 2008). However, as hypothesised, a significant three-way interaction of cannabis use, schizophrenia diagnosis and condition was observed for RT. This interaction was then further interpreted via contrast analysis.

When comparing cannabis users (HC+C and SZ+C) with non-users (HC-C and SZ-C) and schizophrenia patients (SZ-C and SZ+C) with healthy controls (HC-C and HC+C) there was no difference in the sensitivity for high magnitude cues as reflected in the reduction of RT. A very different picture emerged when the interaction of cannabis use and schizophrenia on this behavioural measure was studied. Increased sensitivity to high magnitude cues manifested as an increase in speed (reduction in mean RT) clearly dissociated the different groups. Sensitivity was increased in HC+C and SZ-C compared to HC-C and SZ+C. The increase in reward and punishment sensitivity that was observed for control cannabis users versus control non-users is in accordance with the first hypothesis and supports the notion of reward hypersensitivity in chronic cannabis use (Nestor et al., 2010).

It was observed that chronic cannabis-user patients showed a decrease instead of the expected increase, in incentive-related sensitivity compared to non-user patients. The net null effect of schizophrenia on reward and punishment sensitivity was an increase in patient non-users and a decrease in patient users. While the net null effect of schizophrenia was obtained as stated in the second hypothesis, this was in the reverse direction to that stated in the third hypothesis.

4.3 Incentive anticipation activates reward and punishment-related regions

Initial imaging analyses confirmed that reward and punishment anticipation activated key mesocorticolimbic anatomical structures. While presentation of an incentive cue during the valence period was associated with higher thalamic activation than when a neutral cue was presented, mesocorticolimbic activation was at its peak during incentive trials when the magnitude cue was presented. During this period, activation of thalamus, NAcc, caudate and insula was higher for incentive trials compared to neutral, in accordance with previous studies (Oldham et al., 2018; Liu et al., 2011). Thus, even when comparing the same trials, activation

was higher in reward and punishment-related ROIs during presentation of the magnitude cue than the valence cue. This can be explained by the fact that it is not until presentation of the magnitude cue that the participant has been presented with all of the information about the current trial. Having a complete picture of what is at stake could increase incentive anticipation response and motivation to succeed.

The highest activation however was observed during presentation of a high magnitude cue which resulted in further activation of the same ROIs as well as amygdala signifying the importance of scale of the reward or punishment during the anticipatory period.

Each of these structures has been shown to play a vital role in incentive response. The NAcc, located in the VS, has been described as the central component of the reward system (Shany et al., 2019); the VTA fires dopamine to this area when an incentive is perceived. While some studies have suggested that the NAcc is more sensitive to reward than punishment (Knutson et al., 2001) others have attributed its importance to both appetitive and aversive stimuli (Oldham et al., 2018). Recruitment of NAcc has been shown to occur during anticipation of salient stimuli (Zink et al., 2004) and activity in this area has been linked to various cognitive and motivational processes implicated in the current task including effort, sustained attention and initiation of behaviour (Boureau & Dayan, 2011; Salamone & Correa, 2012).

The caudate, also part of the (dorsal) striatum, receives signals of expected value from the NAcc which in turn initiates a motor response in order to achieve optimal outcome (Balleine et al., 2007; O'Doherty et al., 2004). Activation of the thalamus has been shown to reflect an 'alerting' response, converging with insular information to guide ventral striatal action selection (Cho et al., 2013).

Some studies have found the amygdala to only be associated with loss anticipation, however a recent meta-analysis also found this structure to be recruited in appetitive anticipation (Oldham et al., 2018). The authors suggest that the response is to stimulus arousal rather than valence which in turn increases attention toward the stimuli in order to maximise performance.

Finally, the anterior insula has been found to be involved in the assessment of risk and outcome uncertainty for upcoming events (Bossaerts et al., 2010). This can be explained by the fact that until the participant receives feedback at the end of the trial they cannot be certain of the outcome.

4.4 Chronic cannabis-users display increased activation for reward compared to punishment

There was an activation difference between cannabis users (HC+C and SZ+C) and non-users (HC-C and SZ-C), such that users displayed higher activation in the right putamen, right ventral anterior insula and right dorsal anterior insula for reward compared to punishment trials, in accordance with previous research findings of increased neural sensitivity to reward over punishment (Filbey et al., 2013). This is fitting with the theory that individuals with substance use disorders show a preference for immediate rewards at the cost of future losses, e.g. a cannabis user continues using the substance due to the short-term rewarding effects that the substance has with little deliberation of negative consequences such as addiction, cognitive difficulties, depression, anxiety, insomnia, psychosis etc. It has been suggested that substance users possess a hyperactive mesocorticolimbic system and a hypoactive punishment-avoidance circuitry (Solomon & Corbit, 1973; Bechara et al., 2005; Bickel et al., 2007) and that altered striatal activity may result in a hyperactive response to all forms of reward (Nestor et al., 2010). This may explain why cannabis users have been found

to have higher incidences of gambling (Toneatto & Brennan, 2002; Petry & Tawfik et al., 2001), sexual risk (Castilla et al., 1999) and use of other illicit drugs (Lessem et al., 2006). It is therefore possible that such mesocorticolimbic hyperactivity for all types of reward is what drives individuals to initially seek out cannabis.

Forming part of the dorsal striatum the putamen, like the caudate is concerned with action selection in achieving optimal outcome and has previously been found to be differentially activated in chronic users of cannabis in response to reward, relative to controls (Nestor et al., 2010; van Hell et al., 2010).

4.5 Chronic cannabis use is associated with mesocorticolimbic activity increase in healthy controls and decrease in schizophrenia patients

The increase in activation for high magnitude cues compared to low and neutral ones in left ventral anterior insula, left dorsal anterior insula and bilateral posterior insula was larger in HC+C and SZ-C compared to HC-C and SZ+C replicating the results that were observed behaviourally.

The increase in activation related to reward and punishment anticipation for control cannabis users compared to non-users confirms our first hypothesis and is in accordance with previous research (Nestor et al., 2010). However in contrast to our third hypothesis we observed increased activation for high magnitude cues in non-user patients and a decrease in activation for chronic user schizophrenia patients. These opposing effects compensated for each other resulting in a net null effect of schizophrenia and is in accordance with our second hypothesis as well as previous studies of schizophrenia patients receiving atypical antipsychotics (Schlagenhauf et al., 2008; Juckel et al., 2006b). Again it is important to note here that all of these previous studies have not included chronic cannabis use as a factor in the analysis of reward-related sensitivity in schizophrenia.

The majority of research on the involvement of insula on reward and punishment anticipation has focused on the anterior sub-region (Oldham et al., 2018; Liu et al., 2011), which has been found to be involved in the assessment of risk for upcoming events (Bossaerts et al., 2010) as discussed above. Previous studies have shown functional activation differences of chronic cannabis users (Kober et al., 2014) and schizophrenia patients (Wylie & Tregellas, 2010) compared to controls in the anterior insula but the combined effects of both groups on activation of this area were not investigated. In the current study we observed an interaction effect of cannabis use and schizophrenia on incentive anticipation-related activation in both anterior and posterior insula. Previous research has suggested that increased activity of posterior insula during reward anticipation may indicate increased somatosensory arousal (Yoon et al., 2015). The present study showed a specific increase in activation of the left anterior and bilateral posterior insula in relation to high magnitude cues in HC+C and SZ-C compared to HC-C and SZ+C reflecting a sensitisation of these reward and punishment-related areas by chronic cannabis use and schizophrenia that diminished when both factors were present. It can be said therefore that HC+C and SZ-C attribute greater upcoming risk resulting in greater somatosensory arousal for high magnitude trials compared to low and neutral ones than do HC-C and SZ+C.

4.6 A reward-specific sensitivity?

In this study we observed an increase in right thalamic activation for reward versus punishment cues in HC+C and SZ-C compared to HC-C and SZ+C. This interaction effect once again suggests a reward-specific sensitisation produced by chronic cannabis use and schizophrenia that was reversed when both factors were present. Firstly, this further confirms the theory that healthy cannabis users attribute higher value to reward compared to punishment trials. Secondly, due to the fact that no overall differences were observed between patients (SZ-C and SZ+C) and controls (HC-C and HC+C), the existence of a

significant three-way interaction in thalamic activation for reward compared to punishment trials suggests that patient non-users attribute more value to reward trials which is not true of patients who use cannabis. This again, nullifies any reward-related activation differences between schizophrenia patients and healthy controls. Schizophrenia patients may have a hyperactive reward response in comparison to punishment in a similar way to that of control cannabis users, which then dissipates with the presence of chronic cannabis use.

4.7 Cannabis use increases reward and punishment sensitivity in healthy controls and decreases sensitivity in schizophrenia patients

The striking similarity in the pattern of behavioural and neural effects for the three-way interaction of cannabis, schizophrenia and reward/punishment modulation could lead to the theory that the chronic use of cannabis in healthy controls (HC+C) and in schizophrenia with no comorbid cannabis use (SZ-C) both increase sensitivity to incentive anticipation compared to healthy control non-users (HC-C) manifested in behaviour (speed of decision processing) and neural activation of reward and punishment processing areas. Furthermore the chronic use of cannabis in schizophrenia patients (SZ+C) seems to restore this increased sensitivity to levels similar to those observed for control non-users (HC-C). Interestingly, a prior study has shown that the administration of oral cannabis and THC to schizophrenia patients, can regulate a general dysconnectivity of the mesocorticolimbic circuit (Fischer et al., 2014) and acute administration of CBD has been shown to reduce insular activation during incentive anticipation in individuals at clinically high-risk of developing psychosis (Wilson et al., 2019). CBD has been shown to display neuroprotective properties against the toxic effects of THC (Demirakca et al., 2011) and psychosis-related complications are also more likely to occur following the chronic use of high potency cannabis, defined by the higher concentration of THC. Future studies are thus needed to investigate the differential effects of THC and CBD on reward and punishment anticipation sensitivity in schizophrenia.

Schizophrenia patients have previously been found to display increased reward sensitivity to high but not low magnitude cues in comparison to neutral ones (Waltz et al., 2010). Likewise, the reward sensitised groups (HC+C and SZ-C) in the current study exhibit increased sensitivity specifically to high magnitude.

As discussed in the introduction, a body of research has suggested that cannabis-using and non-using schizophrenia patients are two different groups and schizophrenia patients who have a history of cannabis use may have developed the disorder via a different pathway. Differences in the anticipation of reward and punishment presented here contribute to the mounting research distinguishing schizophrenia patients with a history of cannabis use from those with no history of substance use.

4.8 Limitations

4.8.1 Sample

The division of our sample into four sub-groups and the specific criteria for inclusion in each group resulted in a reduced number of participants for each individual group. While we see highly significant effects using this sample, increasing the number of participants within each group could result in the emergence of additional significant effects especially concerning the interaction of cannabis and schizophrenia on activation of reward and punishment-related areas. Additionally, while we see a main effect of condition in mesocorticolimbic regions, increasing the number of participants may yield significant main effects of condition on RT across all groups resulting in reward and punishment anticipation modulating RT in a similar way to the observed modulation of reward and punishment-related neural regions.

4.8.2 Medication

Between-group differences in antipsychotic medication dosage were controlled for in the current study. All patients were medicated and the vast majority received atypical neuroleptics. Previous research has demonstrated a nullifying of between-group differences in the MID task between schizophrenia patients and healthy controls when the patient group were receiving atypical antipsychotic medication (Juckel et al., 2006b; Schlagenhauf et al., 2008). This can explain our finding of no differences between patients (SZ-C and SZ+C) and healthy controls (HC-C and HC+C). Typical neuroleptics have been associated with reduced ventral striatal activation in response to incentive anticipation (Juckel et al., 2006b), thought to be due to their increased D_2 receptor blockade (Kapur & Seeman, 2001). Furthermore, cannabis produces its effects by targeting the dopaminergic system (Tanda et al., 1997) which is additionally influenced with the receipt of neuroleptic medication (Li et al., 2016). Patient cannabis users have also been found to have poorer response to antipsychotic medication as well as being associated with a greater number of antipsychotic medications being prescribed (Patel et al., 2016).

The difference in behavioural and neural reward and punishment sensitivity between the two groups of patients cannot be readily attributed to medication. However the interacting effects of cannabis and different antipsychotic medications on the dopaminergic system are not fully understood. In order to isolate the effects of cannabis on the mesocorticolimbic system, the current study should be replicated in antipsychotic naïve patients.

4.8.3 Self-reporting and cannabis potency

Finally, all habitual cannabis use data were collected by way of self-report measures in the current study. Due to the fact that self-reports may not be fully accurate combined with the fact that many participants reported regularly using multiple cannabis varieties, potency

data was not included in analysis. Cannabis is a complex substance and many different strains of recreational cannabis are available.

Individuals with psychotic disorders have been found to display alterations of the endocannabinoid system in comparison to healthy controls (Leweke et al., 1999; Reuter et al., 2017). Differences in CB_1 receptor availability in patients relative to controls have also been observed (Borgan et al., 2019) with a general consensus of the involvement of the endocannabinoid system in the pathophysiology of psychotic disorders (Leweke et al., 1999; Ranganathan et al. 2016).

Given the differences in the endocannabinoid system in patients relative to controls; the different effects of THC and CBD, discussed in the introduction; as well as the involvement of the endocannabinoid system in reward processing (Solinas et al., 2007), the effects of cannabis potency and the effects of these two components on the mesocorticolimbic system in schizophrenia should be identified in order to isolate the different effects that these two most abundant constituents of recreational cannabis have in schizophrenia.

4.9 Future directions

As discussed above, conflicting effects of antipsychotic medication as well as the most abundant exogenous endocannabinoids may have had some effect on the results of the current study. A future study of antipsychotic naïve schizophrenia patients with a past history of cannabis use following a period of abstinence, divided in two groups: one receiving oral THC and the other oral CBD could more accurately isolate the true effects of each of these components of recreational cannabis.

A further avenue of research could assess the influence of cannabis on the behavioural and neural effects of receipt of reward in schizophrenia on the same task in order to gain a more complete picture of the entire reward and punishment process.

4.10 Conclusion

Chronic cannabis use and schizophrenia are both associated with alterations to the dopaminergic and endocannabinoid systems which in turn results in alterations to the mesocorticolimbic pathway reflected in motivational differences of individuals from either of these populations. Until now, no research has investigated the combined effects of these factors on the reward/punishment response, be it behavioural or neural.

The study provides evidence for an increase in incentive-related sensitivity in healthy control chronic cannabis-users and schizophrenia patients with no history of cannabis use, reflected in a reduction of RT and increased neural activation of reward and punishment-related regions during incentive anticipation when compared to healthy control non-users and patients with a history of cannabis use. Further evidence is provided for the complex interaction of chronic cannabis use and schizophrenia on the reward/punishment system. The remarkable similarity of between-group differences in both the behavioural and neuroimaging results undoubtedly displays the neural underpinnings of reward and punishment-related behaviour in this sample.

The conflicting effects of both THC and CBD as well as antipsychotic medication on the dopaminergic and endocannabinoid systems affecting the functionality of the mesocorticolimbic pathway complicates the key findings and future research should focus on isolating these differential components.

These results highlight the importance of chronic cannabis use in the investigation of the reward system in schizophrenia and the need for further research in this specific group of

patients, paving the way for an increased understanding of the role that chronic cannabis consumption plays in reward and punishment anticipation in schizophrenia.

Glossary

2-AG	2-arachidonoyl-glycerol
AAL3	Automated anatomical labeling atlas 3
ACC	Anterior cingulate cortex
AEA	*N*-arachidonoyl-ethanolamine
AM251	*N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BOLD	Blood oxygen level dependent
CBD	Cannabidiol
CB_1	Cannabinoid receptor 1
CB_2	Cannabinoid receptor 2
CNS	Central nervous system
D_2	Dopamine receptor 2
dAI	Dorsal anterior insula
FWE	Family-wise error
GLM	General linear model
HC-C	Healthy control non-cannabis users
HC+C	Healthy control cannabis users
HP	High punishment
HR	High reward
LDR	Larger delayed reward
LP	Low punishment
LR	Low reward

MCQ	Monetary choice questionnaire
MID	Monetary incentive delay
MNI	Montreal Neurological Institute
NAcc	Nucleus accumbens
NT	Neutral
PANSS	Positive and negative syndrome scale
pI	Posterior insula
ROI	Region of interest
RT	Reaction time
SIR	Smaller immediate reward
SZ-C	Schizophrenia patient non-cannabis users
SZ+C	Schizophrenia patient cannabis users
THC	Δ^9–tetrahydrocannabinol
vAI	Ventral anterior insula
VS	Ventral striatum
VTA	Ventral tegmental area

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Interaction of schizophrenia and chronic cannabis use on reward anticipation sensitivity

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Chronic cannabis use and schizophrenia are both thought to affect reward processing. While behavioural and neural effects on reward processing have been investigated in both conditions, their interaction has not been studied, although chronic cannabis use is common among these patients. In the present study eighty-nine participants divided into four groups (control chronic cannabis users and non-users; schizophrenia patient cannabis users and non-users) performed a two-choice decision task, preceded by monetary cues (high/low reward/punishment or neutral), while being scanned using functional magnetic resonance imaging. Reward and punishment anticipation resulted in activation of regions of interest including the thalamus, striatum, amygdala and insula. Chronic cannabis use and schizophrenia had opposing effects on reward anticipation sensitivity. More specifically control users and patient non-users showed faster behavioural responses and increased activity in anterior/posterior insula for high magnitude cues compared to control non-users and patient users. The same interaction pattern was observed in the activation of the right thalamus for reward versus punishment cues. This study provided evidence for interaction of chronic cannabis use and schizophrenia on reward processing and highlights the need for future research addressing the significance of this interaction for the pathophysiology of these conditions and its clinical consequences.

npj Schizophrenia (2021) 7:33 ; https://doi.org/10.1038/s41537-021-00163-2

INTRODUCTION

The chronic use of cannabis increases the risk of developing schizophrenia[1]. This risk increases with rising total exposure to cannabis[2]. Chronic cannabis use has been associated with younger age of psychosis onset and there is evidence of a positive correlation between age of chronic use onset and age of psychosis onset[3]. Furthermore, a younger age of psychosis onset has been associated with chronic use of high-potency cannabis on a daily basis[3].

The incidence of chronic cannabis use is greater in patients with schizophrenia compared to the general population[4]. Chronic cannabis user patients have a higher risk of psychotic relapse, more hospital admissions and a higher duration of hospital stay, as well as increased usage of antipsychotic medication[5]. On the other hand, it has been shown that chronic cannabis-using patients perform better than non-using patients in cognitive tests[6–8]. At the neural level patients who use cannabis have been shown to display differences in functional brain activation compared to non-user patients in a variety of domains including emotional memory and visuospatial tasks[9,10].

Differences in reward processing have been demonstrated in both chronic cannabis users and schizophrenia patients. Some studies have shown that chronic users of cannabis have reduced sensitivity to non-drug-related rewards[11]. The effects of reward on cognitive processing have been studied using variations of the monetary incentive delay (MID) task in which reward and/or punishment anticipating cues are followed by a delayed response[12–15]. Using the MID task, studies have reported no reward-related differences in reaction time (RT) amongst users and non-users[11,16–19]. Some studies have reported hypersensitivity in the striatum while anticipating reward and punishment, a reflection of a hypersensitive mesolimbic reward system response to all types of reward in chronic cannabis users[16]. It is not known whether the use of cannabis induces this hypersensitivity or whether it is inherent in some individuals, driving them to seek out cannabis and other types of reward[16]. However, other studies have shown cannabis use to have no effect on neural response to reward and punishment anticipation[17,18] and yet another study showed hypo-activation in some regions, e.g., the caudate[11]. Differential activation patterns of valence type have also been reported, with cannabis users displaying an increase in ventral striatal activation for reward compared to punishment, while healthy controls exhibited the opposite effect[19].

Some studies using the MID task in schizophrenia have reported smaller differences in RT for incentive than non-incentive trials in patients compared to controls[20,21], however others have reported no group differences[22–24]. At the neural level, some studies showed hypo-activation of reward-related brain regions during anticipation of reward[25,26]. Such hypo-activation has been observed in antipsychotic naïve individuals and those treated with typical antipsychotics but has been shown to normalise in those treated with atypical antipsychotics[24,27,28]. Studies have also reported a reduction in striatal activation to be associated with negative symptomatology[20–23,29].

To the best of our knowledge, the combined effects of chronic cannabis use and schizophrenia on reward-related behaviour and

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Table 1. Demographic data for the eighty-three participants that were included in the behavioural analysis.

Measure	HC−C ($n = 27$)	HC + C ($n = 22$)	SZ-C (n = 21)	SZ + C ($n = 13$)	p
Age (years)	27.82 (4.63)	27.05 (7.72)	30.29 (8.00)	23.92 (4.75)	0.056[a]
Sex (% male)	63	77	81	92	0.16[b]
Education level (years)	15.63 (0.79)	14.64 (1.68)	12.76 (1.86)	13.46 (1.66)	**<0.0001**[a]
Clinical data					
Chlorpromazine equivalent (mg)			522 (410)	829 (538)	0.09[c]
Disorder duration (years)			3.50 (4.18)	1.62 (1.93)	0.13[c]
Number of hospitalizations			1.44 (0.94)	1.09 (0.54)	0.32[c]
Cannabis use					
Lifetime use (times used)	3.2 (5.4)	3443.8 (4949)	0.8 (1.2)	3488.3 (4896)	0.98[c]
Duration of use (years)		7.78 (5.42)		6.67 (4.16)	0.54[c]
Frequency of use (per week)		6.45 (4.16)		8.58 (8.44)	0.33[c]
Age of first use (years)		16.91 (2.09)		15.46 (2.22)	0.06[c]

Duration, frequency and age of first use for HC−C and SZ−C were not reported since most of them did not use cannabis. Lifetime use is an estimation based on duration and frequency of use. All measures apart from sex are equivalent to the mean of the respective group. Parentheses indicate standard deviation. Bold typeface = $p < 0.05$. p values for all cannabis use variables indicate significance for testing differences between HC + C and SZ + C.
HC−C non-cannabis user healthy controls, *HC + C* cannabis-user healthy controls, *SZ−C* non-cannabis user schizophrenia patients, *SZ + C* cannabis-user schizophrenia patients.
[a]Analysis of variance (ANOVA) was used.
[b]Chi-square test was used.
[c]Independent samples *t*-test was used.

functional brain activation have not been studied. While one MID study compared antipsychotic naïve schizophrenia patients with previous or ongoing substance abuse with non-using counterparts, this was not specific to cannabis and the effects of substance use were not the main focus of the study[27].

In the present study, we used a two-choice RT task[30] combined with the MID task to study behavioural and neural responses to anticipated reward and punishment in schizophrenia patients and healthy controls, both with and without a history of chronic cannabis use. Reward anticipation sensitivity effects were measured both behaviourally via changes in RT and accuracy as well as neurally via changes in the activity of reward-related brain areas, with the amount of anticipated reward or punishment. Based on the hypothesis that cannabis sensitizes the reward system of the brain[16] it was expected that chronic cannabis use would result in increased reward-related sensitivity both at the behavioural and neural level in control chronic cannabis users. Based on previous studies we also expected to find no effect in reward sensitivity for schizophrenia patients when considered as a homogenous group. We further hypothesized that this net effect could be the result of hyposensitivity related to the effects of schizophrenia in non-user patients and hypersensitivity related to chronic cannabis use in chronic cannabis user patients.

RESULTS

Demographics

Demographic information for the eighty-three participants included in the behavioural analysis, including cannabis use data is presented in Table 1. The pattern of use was gathered via self-report measures. Non-cannabis user schizophrenia patients (SZ −C) and cannabis user schizophrenia patients (SZ + C) did not differ in total duration of the disorder, the number of hospitalisations nor medication dosage. Cannabis user healthy controls (HC + C) and SZ + C did not differ in lifetime use, nor duration, frequency or age of first use. Minimum lifetime usage for cannabis users (HC + C and SZ + C) users was 208 times, and maximum lifetime usage for non-cannabis users (HC−C and SZ−C) was 15 times. There were no sex differences among the four groups but the effect of age approached significance ($F_{3,79} = 2.63$, $p = 0.056$, $\eta_p^2 = 0.091$). Participants differed significantly in years of education ($F_{3,79} = 12.41$, $p < 0.0001$, $\eta_p^2 = 0.32$). Age and education level were included as continuous covariates in all analyses including group effects.

Behavioural global analysis

There was no significant effect of reward on directional accuracy (DA) ($F_{4,308} = 1.78$, $p = 0.132$, $\eta_p^2 = 0.022$). There was no significant interaction of reward x cannabis use ($F_{4,308} = 1.54$, $p = 0.19$, $\eta_p^2 = 0.019$), no significant interaction of reward x schizophrenia ($F_{4,308} = 1.6$, $p = 0.174$, $\eta_p^2 = 0.02$) and no significant three-way interaction of reward x cannabis x schizophrenia ($F_{4,308} = 2.04$, $p = 0.088$, $\eta_p^2 = 0.026$) on DA.

The effect of reward on RT was not significant ($F_{4,308} = 0.86$, $p = 0.485$, $\eta_p^2 = 0.011$) and there was no significant interaction of reward × cannabis use ($F_{4,308} = 0.66$, $p = 0.617$, $\eta_p^2 = 0.008$) nor reward × schizophrenia ($F_{4,308} = 0.61$, $p = 0.659$, $\eta_p^2 = 0.008$). There was however a highly significant three-way interaction of reward x cannabis x schizophrenia ($F_{4,308} = 3.03$, $p = 0.017$, $\eta_p^2 = 0.038$) on RT. The global analysis was also performed on the seventy-three individuals that were retained in the imaging analysis and the results were similar (not presented).

Behavioural contrast analysis

Results from the global analysis revealed significant interactions only for RT. For this reason, only this measure was further investigated in the contrast analysis. The valence contrast was not modulated by cannabis use ($F_{1,77} = 1.23$, $p = 0.27$, $\eta_p^2 = 0.016$), neither by schizophrenia ($F_{1,77} = 0.19$, $p = 0.66$, $\eta_p^2 = 0.002$), nor their interaction ($F_{1,77} = 0.53$, $p = 0.47$, $\eta_p^2 = 0.007$). The reward versus punishment contrast was not modulated by cannabis use ($F_{1,77} = 0.002$, $p = 0.97$, $\eta_p^2 = 0.0002$) nor by schizophrenia ($F_{1,77} = 1.4$, $p = 0.24$, $\eta_p^2 = 0.018$) but was significantly modulated by their interaction ($F_{1,77} = 4.57$, $p = 0.036$, $\eta_p^2 = 0.056$). This effect was however not retained when using the 73 individuals of the imaging sample ($F_{1,67} = 2.98$, $p = 0.088$, $\eta_p^2 = 0.042$). Finally the magnitude contrast was not significantly modulated by cannabis ($F_{1,77} = 0.27$, $p = 0.60$, $\eta_p^2 = 0.033$) nor schizophrenia ($F_{1,77} =$

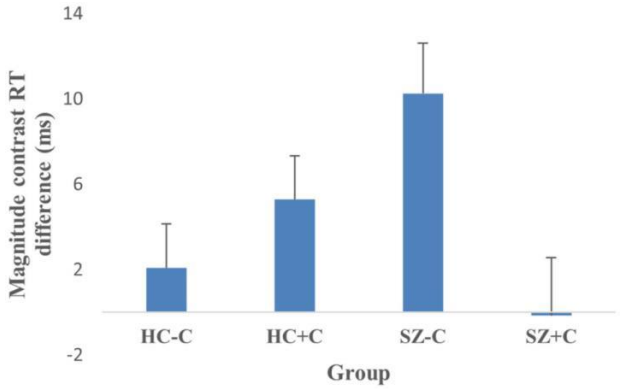

Fig. 1 Reaction time (RT) differences between groups. Mean RT difference (ms) for magnitude contrast for each group. ms milliseconds, HC−C non-cannabis user healthy controls, HC + C cannabis-user healthy controls, SZ−C non-cannabis user schizophrenia patients, SZ + C cannabis-user schizophrenia patients. Error bars indicate standard errors of the mean differences.

their interaction ($F_{1,77}$ =7.64, p=0.007, η_p^2= 0.09). This effect was also retained when using the seventy-three individuals of the imaging sample ($F_{1,67}$ =8.86, p=0.004, η_p^2 = 0.117). Figure 1 shows that the magnitude contrast in RT (corresponding to an increase in speed for the high reward and punishment magnitude cues compared to low magnitude and neutral cues) was larger in HC + C compared to HC−C, while the opposite effect was observed for schizophrenia patients, namely a decrease for SZ + C compared to SZ−C.

Imaging validation analysis

Table 2 and Fig. 2 present the results of the validation analysis. One-sample *t*-tests across all subjects confirmed that reward-related regions, assessed by region of interest (ROI) analysis, were more highly activated in both the valence and magnitude models, for the valence contrast with right thalamus being more highly activated for incentive conditions compared to neutral during the valence cue period. Additional regions were significantly more highly activated for incentive compared to neutral conditions during the presentation of the magnitude cue including the left: thalamus and ventral anterior insula, right: caudate, as well as bilateral: dorsal anterior insula and nucleus accumbens (NAcc). The magnitude contrast revealed high magnitude cues compared to low magnitude plus neutral ones further activated the right: ventral anterior insula and amygdala and left: caudate. There were no differences in activation for the reward versus punishment contrast in any pre-defined ROI.

Imaging main analysis

Based on the results of the validation analysis, the main analysis was carried out on the contrasts for the magnitude model. Between-subjects results of the main analysis including the effects of cannabis, schizophrenia and their interaction are presented in Table 3. There were no between group differences, nor interaction for the valence contrast. The main effect of cannabis use and an interaction of cannabis use and schizophrenia was observed for the reward versus punishment contrast. Extraction of beta values showed an increased activation in the right: putamen, ventral anterior insula and dorsal anterior insula for reward versus punishment for cannabis users (HC + C and SZ + C) compared to non-users (HC−C and SZ−C). Also activation in the right thalamus was larger for reward versus punishment for the HC + C and SZ−C groups versus HC−C and SZ + C groups (Fig. 3a). For the magnitude contrast, there was no main effect of cannabis use nor schizophrenia while the interaction of these two factors appeared for left: ventral anterior insula, dorsal anterior insula and bilateral posterior insula. Following beta value extraction it was shown that HC + C exhibited increased activation in each of the above-mentioned regions compared to HC−C, while the opposite pattern was observed for patients, namely SZ + C displayed activation decreases in all of these regions compared to SZ−C (Fig. 3b).

DISCUSSION

This study investigated the effects of chronic cannabis use and schizophrenia on behaviour and neural activation related to the anticipation of reward and punishment in a two-choice RT task.

There was no overall modulation of DA by reward and punishment and there was no effect on reward-related DA sensitivity of cannabis nor schizophrenia nor their interaction. There was also no overall modulation of RT by reward and punishment and there was no effect on reward-related RT sensitivity of cannabis nor schizophrenia. There was however a significant interaction of cannabis use and schizophrenia. When comparing cannabis users (HC + C and SZ + C) with non-users (HC −C and SZ−C) and schizophrenia patients (SZ−C and SZ + C) with healthy controls (HC−C and HC + C) there was no difference in the sensitivity for high magnitude cues as reflected in the reduction of RT. A very different picture emerged when we studied the interaction of cannabis use and schizophrenia on the behavioural measure of reward sensitivity. Increased sensitivity to high magnitude cues manifested as an increase in speed (reduction in mean RT) clearly dissociated the different groups. Sensitivity was increased in HC + C and SZ−C compared to HC−C and SZ + C. The increase in reward sensitivity that was observed for control cannabis users versus control non-users is in accordance with our first hypothesis and supports the hypothesis of reward hypersensitivity in chronic cannabis use[16]. In contrast to our second hypothesis non-user schizophrenia patients showed increased reward sensitivity compared to non-user controls. Moreover we observed that chronic cannabis user patients showed a decrease instead of the expected increase in reward-related sensitivity compared to non-user patients. In fact the decrease in reward-related sensitivity related to chronic cannabis use fully compensated the increase observed in the non-user patient group resulting in a net null effect of schizophrenia on reward-related sensitivity which is in accordance with previous studies[22–24]. The important factor to consider here is that all these previous studies did not dissociate cannabis user patients from non-users.

Using a version of the MID task we observed an increase of activation in predefined reward-related ROIs, in thalamus, NAcc, caudate and insula for all incentive cues in line with previous studies[31,32]. We also confirmed that high magnitude cues produced a further activation increase in these areas as well as higher amygdala activation, a further important area in reward anticipation[31,33]

The purpose of the study concerned the modulation of reward-related activation by chronic cannabis use and schizophrenia. There was an activation difference between cannabis users (HC + C and SZ + C) and non-users (HC−C and SZ−C), such that users displayed higher activation in the right: putamen, ventral anterior insula and dorsal anterior insula for reward compared to punishment trials, in accordance with previous research showing increased neural sensitivity to reward over punishment[19].

A much more interesting picture emerged when considering the interaction of cannabis and schizophrenia on reward-related activation. The increase in activation for high magnitude cues compared to low and neutral ones in left: ventral anterior insula, dorsal anterior insula and bilateral posterior insula was larger in HC + C and SZ−C compared to HC−C and SZ + C replicating the results that were observed behaviourally for reward-related

Table 2. Region of interest (ROI) validation analysis for the three contrasts using the valence and magnitude cue models.

Contrast	Anatomical labelling		Statistics			MNI coordinates		
	Label	Hemisphere	*Z*	p(svc)	K_E	*x*	*y*	z
Reward + Punishment > Neutral								
Valence model	Thalamus	R	3.84	0.003	20	9	−7	−2
Magnitude model	dAI	L	4.24	0.001	38	−33	23	−2
		R	3.39	0.013	17	42	17	−2
	vAI	L	3.65	0.006	3	−30	20	−5
	NAcc	L	3.33	0.015	5	−3	8	−5
		R	4.60	0.000	25	9	5	−5
	Caudate	R	4.42	0.000	16	9	5	−2
		R	3.28	0.017	3	18	26	1
	Thalamus	L	3.73	0.004	27	−6	−10	−2
		R	3.79	0.003	31	3	−10	1
Reward > Punishment								
Valence model	–	–	–	–	–	–	–	–
Magnitude model	–	–	–	–	–	–	–	–
High > Low + Neutral								
Magnitude model	Caudate	L	4.36	0.000	17	−6	8	−2
		R	4.11	0.001	14	9	5	−2
	NAcc	L	4.26	0.001	29	−6	8	−5
		R	4.38	0.000	12	9	5	−5
	Amygdala	R	4.18	0.001	12	18	−1	−17
	Thalamus	L	3.82	0.003	62	−15	−10	10
		R	3.94	0.002	39	6	−4	4
	dAI	L	3.87	0.002	23	−33	23	−5
		R	4.57	0.000	43	33	23	−8
	vAI	L	3.78	0.003	15	−36	17	−5
		R	4.71	0.000	35	30	20	−11

We applied family-wise error (FWE) correction adjusted for small volume [*p* (svc) < 0.05] within each of the independent ROIs at the voxel level (only ROIs with at least three contiguous voxels were considered significant). There were no significantly different regions for the reward vs punishment contrast.
MNI Montreal Neurological Institute, *svc* small-volume correction, *R* right, L left, K_E number of voxels in cluster, *dAI* dorsal anterior insula, *vAI* ventral anterior insula, *NAcc* nucleus accumbens.

sensitivity. The increase in activation related to reward anticipation for control chronic cannabis users compared to non-users confirms our first hypothesis and is in accordance with the previous research[16]. However in contrast to our second and third hypotheses we observed increased activation for high magnitude cues in non-user patients and a decrease in activation for chronic user schizophrenia patients. These opposing effects compensated for each other so that in the total group of patients there was no difference in reward-related sensitivity when compared to the total group of controls that is in accordance with previous studies of schizophrenia patients receiving atypical antipsychotics[24,25,27]. Again it is important to note here that all of these previous studies have not included chronic cannabis use as a factor in the analysis of reward-related sensitivity in schizophrenia.

The majority of research on the involvement of insula on reward anticipation has focused on the anterior sub-region[31,32], which has been found to be involved in the assessment of risk for upcoming events[34]. Previous studies have shown functional activation differences of chronic cannabis users[35] and schizophrenia patients[36] compared to controls in the anterior insula but the combined effects of both groups on activation of this area were not investigated. In the current study we observed an interaction effect of cannabis use and schizophrenia on reward anticipation-related activation on both anterior and posterior insula. Previous research has suggested that increased activity of the posterior insula during reward anticipation may indicate increased somatosensory arousal[37]. The present study showed a specific increase in activation of the left anterior and bilateral posterior insula in relation to high magnitude cues in HC + C and SZ−C compared to HC−C and SZ + C suggesting a sensitization of these reward anticipation-related areas by chronic cannabis use and schizophrenia that diminished when both factors were present.

In response to valence anticipation, thalamic activation has been found to signify an "alerting" response, converging with insular information to guide action selection in NAcc[38]. In this study we observed an increase in right thalamic activation for reward versus punishment cues in HC + C and SZ−C compared to HC−C and SZ + C. This interaction effect once again suggests a reward-specific sensitization produced by chronic cannabis use and schizophrenia that was reversed when both factors were present.

The striking similarity in the pattern of behavioural and neural effects for the three-way interaction of cannabis, schizophrenia and reward modulation could lead to the hypothesis that the chronic use of cannabis in healthy controls (HC + C) and schizophrenia without a history of cannabis use (SZ−C) both increase sensitivity to reward anticipation compared to healthy control non-users (HC−C) manifested in behaviour (speed of decision processing) and neural activation of reward processing areas. Furthermore the chronic use of cannabis in schizophrenia

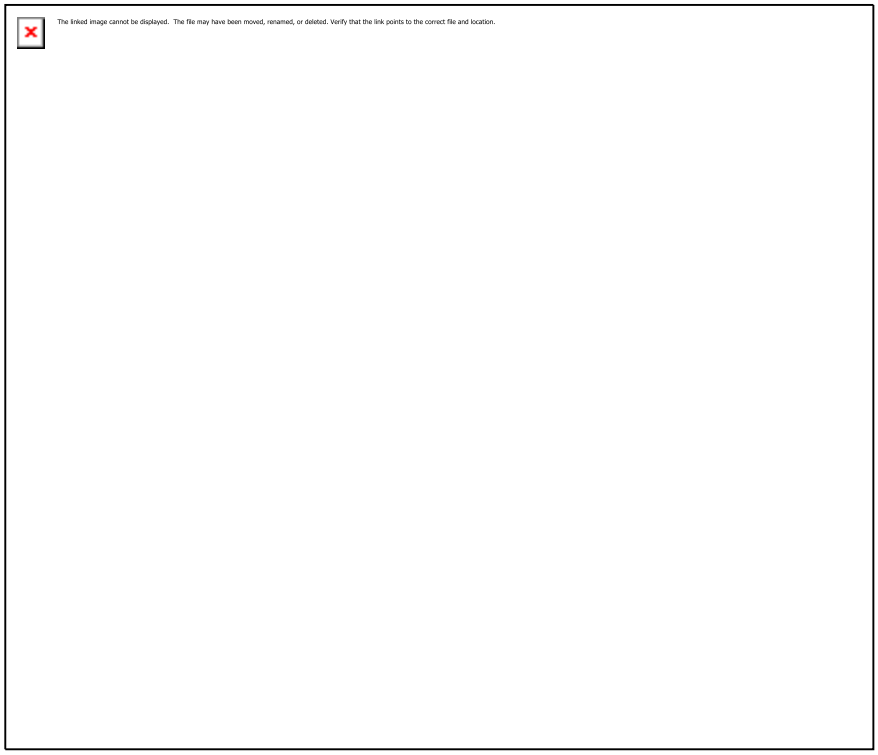

Fig. 2 Validation analysis. Clusters of higher activation for reward + punishment versus neutral conditions for the valence (**a**) and magnitude (**b**) cue period as well as high versus low + neutral for the magnitude cue period (**c**). Clusters thresholded at $p < 0.005$ for visualisation purposes. Red = thalamus; green = caudate; cyan = nucleus accumbens; peach = amygdala; brown = dorsal anterior insula; yellow = ventral anterior insula.

patients (SZ + C) seems to restore this increased reward sensitivity to levels similar to those observed for control non-users (HC−C). Interestingly, a prior study has shown that the administration of oral cannabis and Δ^9–tetrahydrocannabinol (THC) to schizophrenia patients, can regulate a general dysconnectivity of the reward circuit[39] and acute administration of cannabidiol (CBD) has been shown to reduce insular activation during reward anticipation in individuals at clinically high-risk of developing psychosis[40]. CBD has been shown to display neuroprotective properties against the toxic effects of THC[41] and psychosis complications are also more likely to occur following the chronic use of high-potency cannabis, defined by the higher concentration of THC. Future studies are thus needed to investigate the differential effects of THC and CBD on reward anticipation sensitivity in schizophrenia.

The division of our sample in four sub-groups and the specific criteria for inclusion in each group resulted in a reduced number of participants for each individual group. While we see highly significant effects using this sample, increasing the number of participants within each group could result in the emergence of additional significant effects especially concerning the interaction of cannabis and schizophrenia on activation of reward-related areas.

The current study included patients that were medicated and the vast majority received atypical antipsychotics. Although the difference in behavioural and neural reward sensitivity between the two groups of patients cannot be readily attributed to medication, the interaction of medication with reward sensitivity remains an issue that needs to be addressed in future studies investigating the effect of chronic cannabis use in un-medicated or never medicated patients.

Finally all habitual cannabis use data were collected by way of self-report measures in the current study. Due to the fact that self-reports may not be fully accurate combined with the fact that many participants reported regularly using multiple cannabis varieties, potency data was not included in analysis although it is known that potency of cannabis is an important factor when considering the effect of cannabis on psychosis. Future studies could address cannabis potency as an additional factor modulating the effect of cannabis on reward-related sensitivity in schizophrenia.

This study provides evidence for the complex interaction of chronic cannabis use and schizophrenia on the reward system showing that control chronic cannabis users and patients with no history of cannabis use have increased reward-related sensitivity compared to both heathy control non-users and patient users. These results highlight the importance of chronic cannabis use in the investigation of the reward system in schizophrenia and the need for further research in this specific group of patients.

METHODS

Participants

Eighty-nine participants completed the study, 40 patients and 49 healthy controls. Patients were recruited from the psychosis unit of the psychiatry department at Eginition Hospital and were diagnosed by trained psychiatrists using the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10)[42] criteria. One patient received a diagnosis of psychosis not otherwise specified (F29), 34 were diagnosed with schizophrenia (F20) and five with brief psychotic disorder (F23) that were later diagnosed with schizophrenia at follow-up. Thirty-eight patients received atypical antipsychotics (risperidone, paliperidone, olanzapine, amisulpride, quetiapine, aripiprazole, clozapine) and two patients (one user and one non-user) received typical antipsychotics (haloperidole, trifluoperazine).

Pattern of cannabis use was defined using self-report measures. Sixteen patients were classified as SZ + C and twenty-four as SZ−C. Twenty-two healthy control participants were classified as HC + C and 27 as HC−C. Both HC + C and SZ + C were required to have used cannabis a minimum of once per week for one year, within the past year. There were a total of

Table 3. Region of interest (ROI) main analysis displaying the effects of cannabis and schizophrenia on each contrast of interest as well as the cannabis by schizophrenia interactions.

Contrast	Anatomical labelling		Statistics			MNI coordinates		
	Label	Hemisphere	*F*	*p* (svc)	K_E	*x*	*y*	*z*
Reward + Punishment > Neutral								
Cannabis	–	–	–	–	–	–	–	–
Diagnosis	–	–	–	–	–	–	–	–
Interaction	–	–	–	–	–	–	–	–
Reward > Punishment								
Cannabis	Putamen	R	15.89	0.009	4	24	5	−2
	vAI	R	14.09	0.017	8	39	14	−8
	dAI	R	14.42	0.015	6	39	17	−8
Diagnosis	–	–	–	–	–	–	–	–
Interaction	Thalamus	R	14.48	0.015	5	3	−19	7
High > Low + Neutral								
Cannabis	–	–	–	–	–	–	–	–
Diagnosis	–	–	–	–	–	–	–	–
Interaction	vAI	L	15.93	0.008	12	−39	−1	−5
	dAI	L	14.46	0.014	3	−39	2	−2
	pI	R	22.81	0.001	19	42	−10	13
		L	16.05	0.008	16	−42	2	−8

We applied family-wise error (FWE) correction adjusted for small volume [*p* (svc) < 0.05] within each of the independent ROIs at the voxel level (only ROIs with at least three contiguous voxels were considered significant).
MNI Montreal Neurological Institute, *svc* small-volume correction, *R* right, *L* left, *vAI* ventral anterior insula, *dAI* dorsal anterior insula, *pI* posterior insula.

38 cannabis users across both groups (HC + C and SZ + C) and 51 non-users (HC−C and SZ−C).

Exclusion criteria for all patients (SZ + C and SZ−C) included diagnosis of neurological, neurodevelopmental or other psychiatric disorders as well as the history of illicit drug use, other than cannabis. Exclusion criteria for healthy controls (HC + C and HC−C) also included current use of prescription medication, history of illicit drug use other than cannabis, and personal or familial history of psychiatric or neurological disorder. Participants were also excluded if they declared having used cannabis in the past 24 h or if they were intoxicated with alcohol. An effort was made to match patients and control participants for age and sex.

At the time of testing all patients (SZ + C and SZ−C) were in a stable phase of disorder (they were not currently experiencing a psychotic episode and positive symptoms were in remission) and treated with antipsychotic medication; no participant received benzodiazepines or beta-blockers on the day of testing. All cannabis users (HC + C and SZ + C) were asked to abstain from using for at least 24 h prior to study completion, and asked again on the day of testing to reduce the likelihood of confounding subacute effects. All participants were presented with a detailed description of the study design to ensure that they fully understood the procedures and gave written informed consent. The study protocol was approved by the ethics committee of Eginition University Hospital and was conducted according to the principles of the Declaration of Helsinki.

Stimuli and procedure

A two-choice RT task was used with elements of the MID and Eriksen flanker tasks. Participants completed the task in one session to reduce the likelihood of learning effects, while being scanned using functional magnetic resonance imaging (fMRI). The participant held a response pad (Cedrus, California, USA) and was instructed to respond to a series of five arrow heads appearing for a fixed period, with their right or left index finger, in accordance with the pointing direction of the central arrowhead. Only the incongruent configuration of the arrow heads was used (< < > < < or > > < > >). Preceding the stimulus, a valence cue was first presented, for a variable period (0.8, 2.8 or 4.8 s), consisting of either + (win), − (lose) or * (neutral), followed by the magnitude cue representing the amount of the upcoming reward (high: 20, low: 5, or none: 0) that was presented for 1 s. After the 1 s response period, feedback was presented for 1.2 s. The participant was informed that the aim of the task was to gain a maximal amount of points and in order for them to win (+) or avoid losing (–), they must respond both accurately and quickly. The task was divided into 6 blocks of 60 trials with the first block consisting solely of neutral trials, used to generate a baseline mean RT from each participant's correctly answered trials. On subsequent blocks, the participant completed a trial successfully if they responded with the correct button-press and faster or equal to their mean RT from the first block. These five blocks each contained twelve trials of each condition (high punishment, low punishment, neutral, low reward, high reward).

Behavioural data acquisition and analysis

DA and RT data were analysed for the five blocks of the reward task. 6 patients (3 SZ−C, 3 SZ + C) were excluded from the behavioural analysis due to a < 70% DA, resulting in a total of eighty-three included participants. DA and RT were recorded for each participant and each condition. We excluded RT < 120 ms, considered as anticipatory responses. Total mean DA and RT were calculated for each condition.

A global analysis was performed for DA and mean RT using the general linear model (GLM) and a 2 × 2 × 5 analysis of covariance (ANCOVA) design. Reward condition was the within-subject repeated measures factor (5 levels) while cannabis use and schizophrenia were between-group fixed factors (2 levels each). Finally education level and age were used as continuous covariates. Since the focus of this study was the interaction of reward effects with cannabis use and schizophrenia we report only the reward-related effects of this analysis and not the main effects of cannabis, schizophrenia and their interaction.

A second analysis was performed to investigate the nature of the significant interaction effects between reward conditions and group factors. Following the same rationale as will be presented subsequently for the analysis of the imaging data we computed three specific contrast values for DA and three for mean RT, for each subject as follows:

- valence: difference between the neutral condition and the mean of all valence conditions
- reward versus punishment: difference between mean of reward and mean of punishment conditions.
- magnitude: difference between the mean of low magnitude plus neutral conditions and the mean of high magnitude conditions.

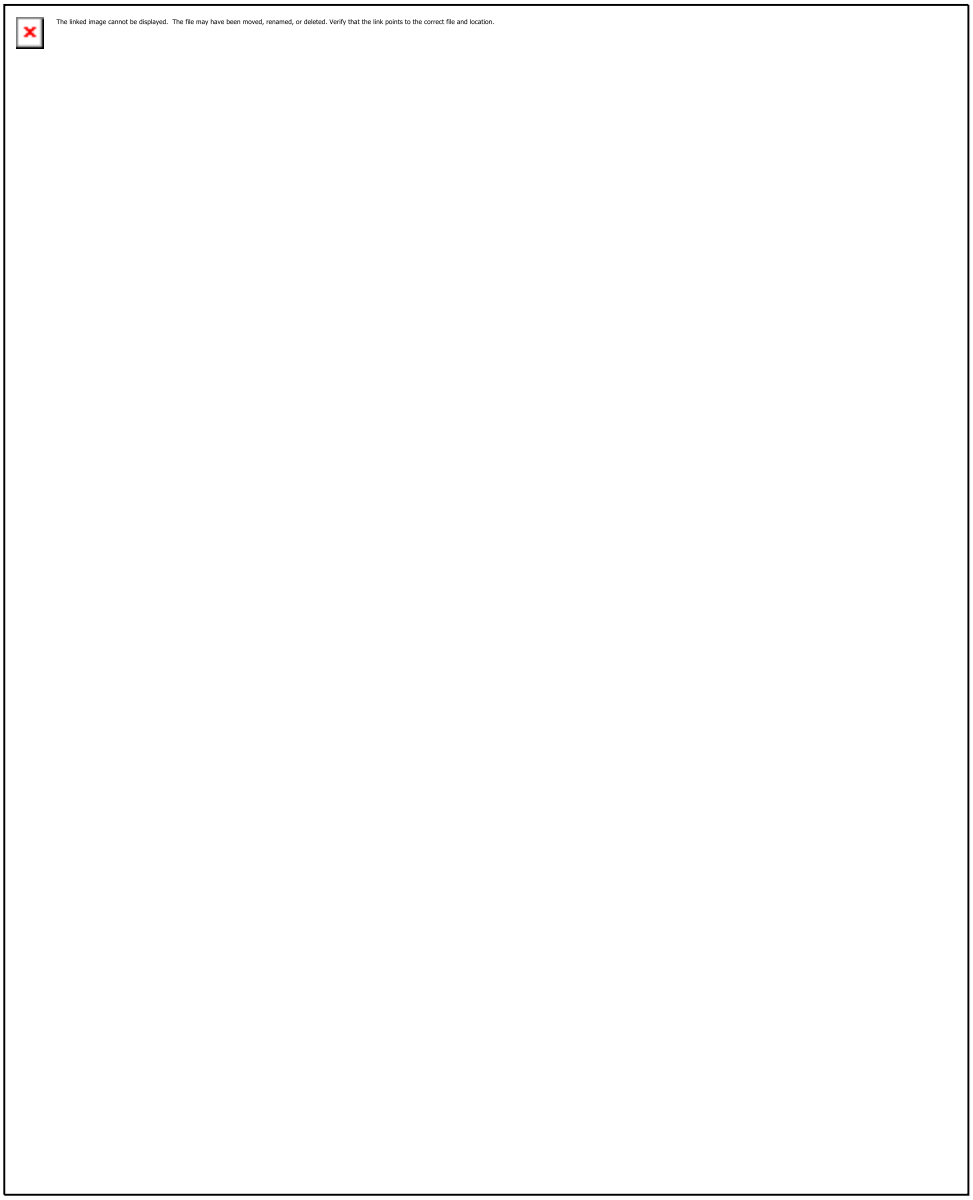

Fig. 3 Main analysis. Clusters showing significant modulation by the interaction of cannabis and schizophrenia for the reward versus punishment contrast (**a**) and the magnitude contrast (**b**). Clusters thresholded at $p < 0.005$ for visualisation purposes. Red = thalamus; yellow = ventral anterior insula; brown = dorsal anterior insula; violet = posterior insula. The bar plots show mean beta values for each cluster for each group and error bars show standard errors of the mean beta values. HC−C non-cannabis user healthy controls, HC + C cannabis-user healthy controls, SZ−C non-cannabis user schizophrenia patients, SZ + C cannabis-user schizophrenia patients.

These contrast values for each subject were used as dependent variables in a GLM 2 × 2 ANCOVA with cannabis use and schizophrenia as fixed factors and years of education and age as continuous covariates.

The GLM tool in Statistica 12 (StatSoft Inc., 1984–2014) was used for all analyses of behavioural data.

fMRI data acquisition and analysis

Functional MR images were acquired using a Philips Achieva 3.0 Tesla TX MRI scanner using echo-planar imaging with 2 s repetition time (TR), 36 slices and 3 × 3 × 3 mm voxel size. A high-resolution T1 anatomical image with 1 × 1 × 1 mm voxel size was also acquired for each participant. Quality control was performed using ArtRepair software (Center for Interdisciplinary Brain Sciences, Stanford University, USA). Ten participants (1 HC−C, 4 HC + C, 4 SZ−C, 1 SZ + C) were excluded due to low image quality, resulting in a sample of seventy-three participants.

SPM12 toolbox for MATLAB (Wellcome Trust Centre for Neuroimaging, London, UK) was used for all imaging data analysis. Pre-processing was first performed by spatially realigning the raw images and temporal interpolation was completed to correct for delay in slice acquisition. Data with registered motion >3 mm or 1 degree was excluded, in keeping with the general rule for exclusion of data with motion greater than the dimensions of a single voxel[43]. The T1 image was next used to segment the images into grey and white matter and cerebrospinal fluid (CSF). Images were normalized to standard Montreal Neurological Institute (MNI) space and smoothed with an 8 mm full width at half maximum (FWHM) Gaussian kernel. The voxel size and smoothing kernel used in our analysis are in accordance with other studies where similar parameters were included in order to study reward processing regions either using whole-brain analysis[44] or ROI-based analysis, including predefined reward regions, i.e., ventral striatum and insular segments[45,46]. A high-pass filter of 128 s cut off was applied, to eliminate physiological components such as respiration or heartbeat.

Onset times for each condition were extracted for both valence and magnitude cues, with the relative duration for each specific trial and cue type. A first-level within-subject analysis was carried out for both valence

and magnitude separately, whereby a GLM was applied to the images from each participant. Three regressors, reward (+), punishment (−) and neutral (*) were included for the valence model. Five regressors (−20, −5, 0, +5, +20) were included for the magnitude model. Additional regressors included motion correction parameters estimated from the realignment step of the pre-processing. T-contrasts were calculated to measure the contrasts of valence, reward versus punishment and magnitude that were defined as previously described. The valence and reward versus punishment contrasts were calculated in the valence model while all three contrasts were calculated in the magnitude model.

At the second-level, a validation ROI analysis was first carried out to verify that reward-related regions were activated during the two cue periods. One-sample *t*-tests were carried out for each contrast. The following ROIs were selected and included in the present study based on a recent meta-analysis of neural activation in the MID task, reporting activation in common regions for reward and punishment anticipation; striatum, thalamus, amygdala and insula[31]. The striatum was divided into subcomponents of NAcc, caudate and putamen and were defined structurally along with thalamus and amygdala, using the Automated Anatomical Labelling atlas 3 (AAL3). Considering the anatomically and functionally distinct insular sub-regions[47] and their involvement in reward tasks[37,48], the insula was divided into sub-regions of dorsal and ventral anterior, as well as posterior. Using mean MNI coordinates from a prior study[47], the insular sub-regions were manually defined on T1[49] in order to ensure the inclusion of all anatomically relevant regions and the exclusion of anatomically irrelevant regions. All ROIs were defined in MNI space for both right and left hemispheres and were defined before any data analysis in order to avoid bias[50]. Activation within each ROI was assessed with an inclusive mask; the analyses were restricted to the previous ROIs for which control for multiple comparisons was performed using Gaussian random field (GRF) theory for small volume[51] which allows for conduct principled correction resorting to the GRF theory within a predefined ROI[52]. Small volume correction (SVC) of sphere with 10 mm radius surrounding the peak voxel was applied within these regions and clusters were considered significant if the family-wise error (FWE) corrected peak *p*-value was significant at $p < 0.05$, as in previous studies[45,53] A minimum cluster size threshold of three contiguous voxels was considered in all analyses to avoid type-1 errors[54]

The main analysis was a 2 × 2 ANCOVA to assess the modulation of each contrast with cannabis use, schizophrenia status and their interaction, with years of education and age as covariates. Using Marsbar, beta values for each significant voxel cluster were extracted for each participant to assess the nature of the interaction by means of plots.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

DATA AVAILABILITY

All the data presented and analysed in this study are fully available from the authors upon request.

Received: 11 January 2021; Accepted: 28 April 2021;
Published online: 16 June 2021

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ACKNOWLEDGEMENTS

S.F. was supported by the IKY Scholarship Program for Non-Greek Nationals (1425). F.C. is supported by the EU-IKY Scholarship Program (European Social Fund-ESF), the Greek "Reinforcement of Postdoctoral Researchers" grant (5033021) of the "Human Resources Development Program, Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF 2014–2020).

AUTHOR CONTRIBUTIONS

S.F., N.S., N.C.S. and N.K. participated in the design of the study. N.S. coordinated the study. S.F. designed the experimental protocol and E.K. designed the imaging sequence protocol. S.F. was responsible for collecting the data for the study and E. K. and G.V. participated in the data collection. S.F., F.C. and N.S. analysed the data and E.K. participated in the pre-processing and quality control of the imaging data. S.F. and N.S. wrote the original draft of the manuscript and F.C., E.K., N.K., N.C.S. and C.K. participated in revising and editing the final manuscript of the study.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41537-021-00163-2.

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