Thinking High

The impact of cannabis on human cognition

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Introduction

Cannabis pharmacology

The first accounts of investigation into the pharmacological effects of *Cannabis sativa* can be found in Chinese oral tradition dating back to 2700 B.C. In the book *Shen Nong Ben Cao Jing*, cannabis was noted to stimulate appetite and produce hallucinatory and antisenility effects (Shou-Zhong, 1997). Modern research on the pharmaceutical properties of the cannabis plant began with the isolation and synthesis of delta-9-tetrahydrocannabinol (THC) by Gaoni and Mechoulam (1964). THC has been found to produce most of the desired psychoactive effects of cannabis through the stimulation of the cannabinoid type 1 receptor (CB_1; Grotenhermen, 2003). This has led to the development of cannabis strains containing high amounts of this compound through the use of modern hydroponic cannabis farms (Hardwick and King, 2008). Consequently, it has been claimed that the availability of THC-abundant cannabis plants could result in more severe effects of abuse, since THC has been connected with the emergence of anxiety (Hunault et al., 2014) and psychotic episodes both in an acute intoxicated state (D'Souza et al., 2004) and in the long-term (Kuepper et al., 2010). However, since the discovery of THC, over 100 other natural compounds, called cannabinoids, have been isolated from the plant (ElSohly and Gul, 2014). Up-to-date research indicates that cannabidiol (CBD), the major constituent of the non-psychoactive (fiber-type) variety of cannabis, produces effects which are in contrast to those induced by THC (Bhattacharyya et al., 2010). CBD has been shown to act as a partial antagonist at CB_1 receptors (Pertwee, 2008) and as an agonist at serotonin receptors (5-HT; Campos and Guimarães, 2008; Zanelati et al., 2010; Gomes et al., 2011). CBD also stimulates the vanilloid receptor type 1 (VR1) with a maximum effect similar in efficacy to that of capsaicin (Bisogno et al., 2001). Moreover, CBD has been shown to have anxiolytic (e.g., Zuardi et al., 1982, 1993; Crippa et al., 2004, 2011; Fusar-Poli et al., 2009; Bergamaschi et al., 2011) and antipsychotic effects in humans (e.g., Zuardi et al., 2009; Bhattacharyya et al., 2010; Schubart et al., 2011). In addition, there is evidence that CBD modulates the effects of THC by affecting its absorption, distribution, and metabolism (McPartland and Russo, 2014).

Aside of cannabinoids, the cannabis plant also contains terpenoids—the compounds responsible for the smell and taste of cannabis (McPartland and Russo, 2014). Terpenoids have been identified to affect the pharmacokinetics of THC by inducing vasodilatation of alveolar capillaries (thus increasing THC absorption by the lungs) and enhancing blood–brain barrier penetrability

(Agrawal et al., 1989). In addition, research points to analgesic, anti-inflammatory, and neuroprotective properties of specific terpenoids present in cannabis (Russo, 2011). In sum, although sufficient research is still lacking, both CBD, as well as terpenoids, can be considered as "entourage compounds" in cannabis, due to their interactions with THC (Russo, 2011; McPartland and Russo, 2014). Consequently, in contrast to many other recreational drugs containing only one active compound, the pharmacological complexity of cannabis makes it more difficult to investigate the psychoactive effects of the plant, as well as a fascinating topic of study that highlights many research opportunities.

Cognitive effects of cannabis

In spite of the abundance of different compounds present in cannabis, THC has been found to have the most significant impact on cognition (Curran and Morgan, 2014). The discovery of the endocannabinoid system through the identification of the CB_1 receptor (Devane et al., 1988; Matsuda et al., 1990) and the first endogenous cannabinoid (anandamide, AEA; Devane et al., 1992) opened the doors for a better understanding of the biological mechanisms behind the cognitive effects of cannabis. Research points to complex pharmacological interactions between the endocannabinoid and dopamine (DA) systems as one of the mechanisms through which THC affects cognitive processes. Specifically, CB_1 receptors, which are widely distributed in the brain, indirectly modulate the release of DA through the inhibition and stimulation of Gamma Amino Butyric Acid (GABA) and glutamate neurons (Gerdeman et al., 2003; Fattore et al., 2010; Fernández-Ruiz et al., 2010). Moreover, research shows that repeated stimulation of CB_1 receptors leads to the decrease in their density in the brains of chronic cannabis users (Hirvonen et al., 2012). As a consequence, the effects which THC has on cognition differ between experienced and infrequent users. In particular, it has been demonstrated that smoking of THC-rich cannabis joints by chronic cannabis users does not lead to impairments in cognitive flexibility, mental calculation, and reasoning (Hart et al., 2001), or in episodic and working memory (Hart et al., 2010). Moreover, although infrequent users have been found to display impaired tracking performance and attentional processes following THC administration, the same has not been observed in regular cannabis users (Ramaekers et al., 2009; Theunissen et al., 2012). Nevertheless, it seems that inhibitory control is

similarly impaired among both populations when intoxicated with cannabis (Ramaekers et al., 2009).

As for CBD, the way that it influences cognition is less clear. Some researchers (e.g. Schier et al., 2012) have claimed that CBD has no effect on cognitive processes. Nonetheless, research shows that CBD has contradictory effects to THC on the activation of brain regions during response inhibition (Borgwardt et al., 2008), emotional processing (Fusar-Poli et al., 2009), and verbal memory (Bhattacharyya et al., 2010). Combining this with the memory-protecting properties of CBD against the impairing effects of THC (Morgan et al., 2010, 2012), it may be claimed that CBD is a potent modulator of the cognitive impact of THC. On the other hand, the data available on the cognitive effects of pure CBD is scarce, aside from a recent study showing enhancement of emotional facial affect recognition after CBD administration (Hindocha et al., 2015).

Outline of this thesis

The main goal of this thesis is to present novel insight into the impact of cannabis on cognitive functions and their neural correlates. Specifically, this thesis contains three empirical chapters and one review chapter on both the acute and chronic effects of cannabis on mental and neural processes.

Chapter 2 investigated the effects of chronic use of cannabis on striatal dopaminergic functioning. In this study, regular cannabis users were compared with non-users controls with regard to their spontaneous eye blink rate (EBR)—an indirect marker of DA transmission in the striatum.

Chapter 3 examined the acute impact of cannabis on creativity. The experiment included chronic users who were administered cannabis with different concentrations of THC using a vaporizer and tested on tasks tapping into divergent and convergent thinking.

Chapter 4 investigated the acute effects of cannabis on the neural correlates of error monitoring. This study investigated how different doses of vaporized THC-rich cannabis affected the amplitudes of two event-related potentials (ERPs) associated with the cognitive processing of errors—the error-related negativity (ERN) and error positivity (Pe).

Chapter 5 reviewed the available neuroimaging research on the impact of CBD on cognitive and emotional processing. In particular, the putative role of the anterior cingulate cortex (ACC) as a critical modulator of the effects of

CBD on brain connectivity was examined and potential implications of ACC involvement were discussed.

Finally, chapter 6 summarizes the results of all the empirical studies presented in this thesis together with the conclusions of the review. In addition, the implications of the results are discussed and suggestions for future research are presented.

The references to the published chapters are presented below:

Chapter 2: Kowal MA, Colzato LS, Hommel B (2011) Decreased spontaneous eye blink rates in chronic cannabis users: evidence for striatal cannabinoid-dopamine interactions. PLoS ONE 6:e26662. DOI: 10.1371/journal.pone.0026662

Chapter 3: Kowal MA, Hazekamp A, Colzato LS, van Steenbergen H, van der Wee NJA, Durieux J, Manai M, Hommel B (2015a) Cannabis and creativity: highly potent cannabis impairs divergent thinking in regular cannabis users. Psychopharmacology 232:1123-1134. DOI: 10.1007/s00213-014-3749-1

Chapter 4: Kowal MA, van Steenbergen H, Colzato LS, Hazekamp A, van der Wee NJA, Manai M, Durieux J, Hommel B (2015b) Dose-dependent effects of cannabis on the neural correlates of error monitoring in frequent cannabis users. European Neuropsychopharmacology 25:1943-1953. DOI: 10.1016/j.euroneuro.2015.08.001

Chapter 5: Kowal MA, Hazekamp A, Colzato LS, van Steenbergen H, Hommel B (2013) Modulation of cognitive and emotional processing by cannabidiol: the role of the anterior cingulate cortex. Frontiers in Human Neuroscience 7. DOI: 10.3389/fnhum.2013.0.

2

The effects of chronic cannabis use on striatal dopaminergic functioning*

* This chapter is based on:

Kowal MA, Colzato LS, Hommel B (2011) Decreased spontaneous eye blink rates in chronic cannabis users: evidence for striatal cannabinoid-dopamine interactions. PLoS ONE 6:e26662. DOI: 10.1371/journal.pone.0026662

Abstract

Chronic cannabis use has been shown to block long-term depression of gamma amino butyric acid (GABA)-glutamate synapses in the striatum, which is likely to reduce the extent to which endogenous cannabinoids modulate GABA- and glutamate-related neuronal activity. The current study aimed at investigating the effect of this process on striatal dopamine levels by studying the spontaneous eye blink rate (EBR), a clinical marker of dopamine levels in the striatum. Twenty-five adult regular cannabis users and 25 non-user controls matched for age, gender, race, and IQ were compared. The results showed a significant reduction in the EBR of chronic users from that of non-users, suggesting an indirect detrimental effect of chronic cannabis use on striatal dopaminergic functioning. Additionally, EBR correlated negatively with years of cannabis exposure, monthly peak cannabis consumption, and lifetime cannabis consumption, pointing to a relationship between the degree of impairment of striatal dopaminergic transmission and cannabis consumption history.

Introduction

Cannabis (*Cannabis sativa*) is the most widely used illicit drug in Europe and the US. Its recreational use dates back to over 2000 B.C. The active compounds in cannabis are called exogenous cannabinoids, with delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) being responsible for most of the drug's psychoactive effects (Earleywine, 2002). Current research indicates that THC, as a cannabinoid CB1 receptor agonist, indirectly affects dopaminergic functioning. Stimulation of the cannabinoid receptor type 1 (CB1) results in the release of dopamine (DA) (Gerdeman et al., 2003)—a neurotransmitter involved in the control of goal-directed behavior, reward learning, reinforcement, and addiction (Fattore et al., 2010). However, CB1 receptors are not present at dopaminergic neurons. Instead, they are located in gamma amino butyric acid (GABA) and glutamatergic terminals which, in turn, influence DA/D1 and DA/D2 neurons by controlling DA inhibition. In other words, CB1 receptors contribute to the release of DA by inhibiting DA inhibitors.

Interestingly, the highest concentrations of CB1 receptors in the brain can be observed at the same areas where dopaminergic neurons are present (Fattore et al., 2010). Crucial regions in this regard seem to be the basal ganglia and, more specifically, the striatum, in which endogenous cannabinoids modulate the firing of DA neurons. This occurs through postsynaptic interactions between cannabinoids and DA at the level of G-protein/adenylyl cyclase signal transduction (Fernández -Ruiz et al., 2010). As a consequence, it makes sense to assume that any effect of THC on DA transmission is the product of an indirect process. This is different from the impact of other often abused drugs, like amphetamine or cocaine, which seem to act directly on DA neurons (for a discussion, see: Colzato et al., 2008).

Hitherto, two studies using positron emission tomography have looked into the acute effect of THC on striatal DA transmission—with, however, inconsistent results: one study reported a THC-induced increase in striatal DA level (Bossong et al., 2009) while another found no effect (Stokes et al., 2009). Things are even less clear with regard to chronic effects of long-term exposure to THC, on which no data are available. This is particularly unfortunate in view of Kuepper's et al. (2010) suggestion that repeated THC administration may create a dopaminergic imbalance in the brain by increasing striatal DA levels but lowering DA levels in the prefrontal cortex. As a possible consequence of this imbalance, chronic THC exposure has been assumed to

induce psychotic symptoms in users (Kuepper et al., 2010). However, a problem with this assumption is that it is not based on any evidence regarding chronic effects of THC on striatal DA transmission, but on only one finding regarding the acute effects level (Bossong et al., 2009). Therefore, it is not clear whether THC actually induces long-term dopaminergic imbalances.

To address this issue, the present study aimed to investigate the effect of long-term exposure to cannabis on striatal DA transmission. In the case of chronic effects, it is difficult to differentiate between the specific psychoactive plant components which caused the potential impairments. Consequently, we use the more generic term "cannabis" in the present study, even though the available data suggest that the observed effects are mainly due to the impact of THC. For one, from the two main studied psychoactive compounds of cannabis, only THC acts as a CB1 receptor agonist, while CBD functions as an antagonist. For another, CBD is suspected to reduce the psychotic effects of THC, which would suggest a role of CBD in diminishing the potential DA-impairing effects of THC (Morgan et al., 2010). Nevertheless, for the sake of precision, no reference to specific cannabinoids is made.

We assessed dopaminergic functioning by means of spontaneous eye blink rates (EBRs), a well-established clinical marker of striatal DA production (Karson, 1983; Shukla, 1985; Taylor et al., 1999). Numerous observations have helped to validate EBR as a measure of striatal DA functioning. For instance, deviant levels of EBR have been reported from patients suffering from DA-related impairments: while EBR is elevated in schizophrenic patients, who exhibit increased striatal DA transmission (Freed, 1980), EBR is lowered in Parkinson's patients, who have a reduced amount of nigrostriatal dopaminergic neurons (Deuschel and Goddemeier, 1998). In addition, EBRs vary as a function of the DRD4/7 genotype, which is associated with the modulation of DA levels in the striatum (Dreisbach et al., 2005). Moreover, nonhuman primate research has shown that direct DA agonists and antagonists increase and decrease EBRs, respectively (Kleven and Koek, 1996).

Exact predictions of how chronic cannabis use might affect the striatal DA level—and the associated EBR—can be derived from animal research. Hoffman et al. (2003) showed that, in rats, chronic treatment with a CB1 receptor agonist results in a reduced sensitivity of CB1 receptors located at glutamatergic and GABAergic terminals. Moreover, chronic application of THC completely blocks long-term depression (LTD) of GABA-glutamate synapses in the striatum. Normally, the regulatory role of LTD is to inhibit the activity of GABA and glutamate neurons and, thus, to block their control over DA

neurons, which again allows for DA transmission. Consequently, blocking LTD should reduce the extent to which endogenous cannabinoids modulate GABA and glutamate neuron activity. Moreover, the LTD–DA relationship appears to be bidirectional: striatal DA neurons are capable of synthesizing endogenous cannabinoids, which induce LTD and interact with DA as a supplementary inhibitory feedback mechanism (Fattore et al., 2010; Fernández-Ruiz et al., 2010). However, in the case of chronic cannabis use, the decreased sensitivity of CB1 receptors implies that the likelihood of endogenous cannabinoids evoking LTD is lowered. As a result of this bidirectional process, chronic application of exogenous cannabinoids present in cannabis could be expected to lead to decreased DA transmission due to long-term, maladaptive inhibition by GABA and glutamate (Hoffman et al., 2003). If so, we would expect a decrease of the spontaneous EBR in chronic cannabis users from that in non-users

Results

EBR per minute was significantly lower in the chronic cannabis users (M = 10.24; SD = 5.861) than in the non-user controls (M = 17.52; SD = 9.019), $t(48) = 3.384$, $p < 0.01$. The same effect was obtained from an ANOVA with group (chronic cannabis users vs. non-user controls) as an independent variable and IQ and cigarette use as covariates: while the group effect was again significant, $F(1, 46) = 5.477$, $p < 0.05$, the covariate effects were not.

To test whether the EBR in the chronic cannabis users was related to their consumption history and habits, Spearman's Rho correlation coefficients were calculated between EBR/minute and the years of cannabis exposure, age of onset, monthly regular, monthly peak, and lifetime cannabis consumption. EBR correlated negatively with years of exposure, $r(25) = -0.42$, $p < 0.05$ (see Figure 1), monthly peak consumption, $r(25) = -0.43$, $p < 0.05$ (see Figure 2), and lifetime consumption, $r(25) = -0.40$, $p < 0.05$ (see Figure 3), while no significant correlations were found for age of onset, $r(25) = -0.04$, p = n.s., and monthly regular consumption, $r(25) = -0.25$, p = n.s.

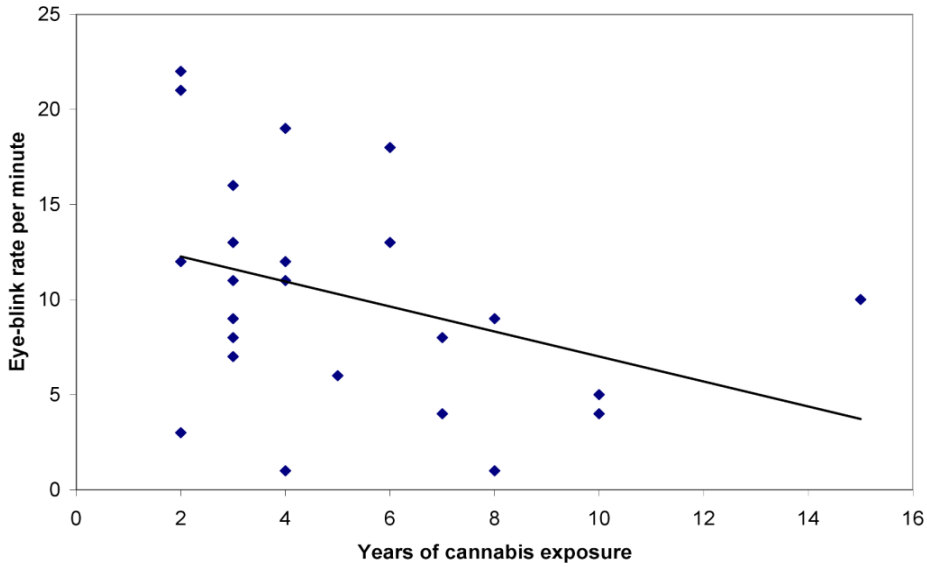

Figure 1 *Years of cannabis exposure as a function of spontaneous eye blink rate per minute.*

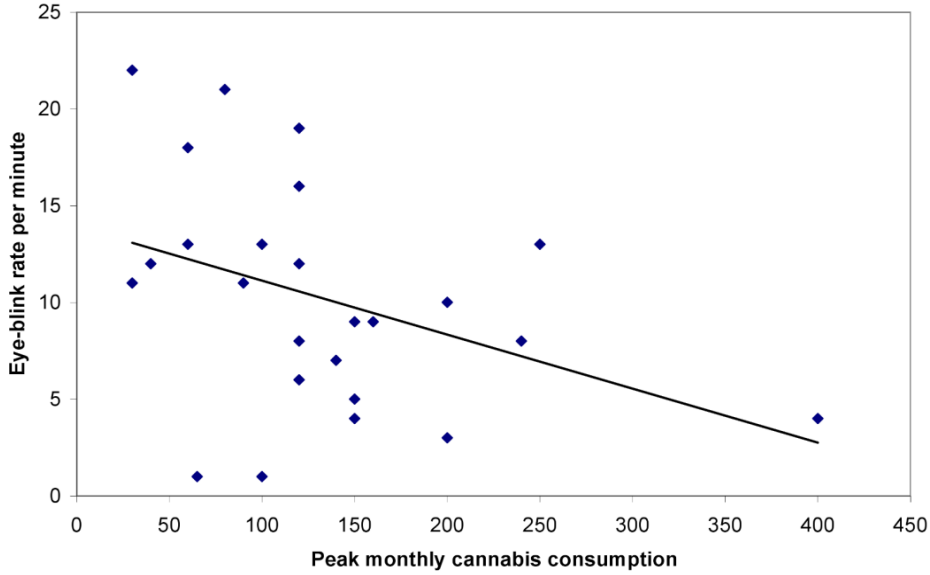

Figure 2 *Peak monthly cannabis consumption (in joints) as a function of spontaneous eye blink rate per minute.*

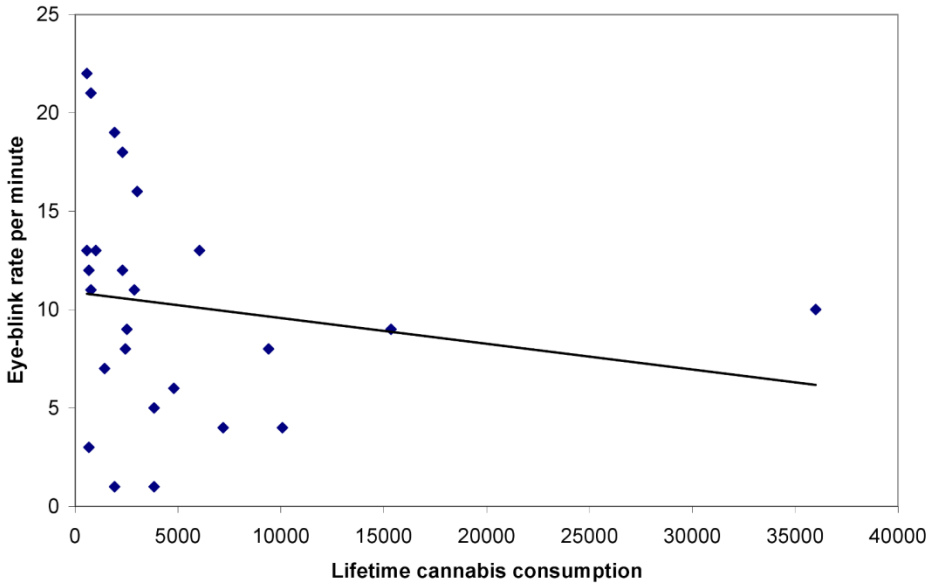

Figure 3 *Lifetime cannabis consumption (in joints) as a function of spontaneous eye blink rate per minute.*

Discussion

The results of the study show a significant reduction of spontaneous EBR in chronic cannabis users from that in non-user controls. This can be interpreted as an indication of a dopaminergic hypoactive state in the striatum (Karson, 1983; Shukla, 1985; Taylor et al., 1999). Additionally, a moderate negative correlation between EBR and years of cannabis exposure suggests that the degree of impairment of DA transmission is, to a certain extent, proportional to the period of cannabis use. Conversely, the lack of a correlation between EBR and the age of onset of cannabis consumption suggests that starting to use marijuana at an earlier age does not contribute to the level of dopaminergic hypoactivity. However, such a claim should be treated with caution due to the fact that adolescent cannabis use has been linked to specific cognitive impairments, like less efficient discrimination between relevant and irrelevant stimuli (Abdullaev et al., 2010). In any case, it can be assumed that the striatal dopaminergic hypoactive state of chronic cannabis users is the result of blocking the supplementary inhibitory mechanism of LTD. The impairment of GABA and glutamate neuron activity combined with the downregulation of CB1 receptors seem to be plausible explanations for the

observed decreased EBR in chronic users (Hoffman et al., 2003; Fattore et al, 2010; Fernández-Ruiz et al., 2010).

In the case of the modest negative correlation between EBR and monthly peak cannabis use, it could be inferred that a more pronounced binge use of marijuana has an additional detrimental impact on the level of DA in the striatum. However, DA impairment was found not to be related to the regular amount of cannabis consumed per month. A possible explanation for this effect comes from the research by Bolla et al. (1998), who identified organic drug exposure intensity, instead of duration, as a key factor in developing drug-related neurocognitive deterioration. Therefore, it seems plausible to assume that binge use of cannabis is a better predictor of DA impairment than regular consumption is. Additionally, the moderate negative correlation between EBR and lifetime cannabis consumption suggests that the degree of impairment of striatal dopaminergic functioning is related to the total amount of cannabis consumed during a lifetime. Possibly, use of higher doses of cannabis, both in the short- and long-term, has a more detrimental enduring effect on GABA and glutamate inhibition of DA in striatum than the impact of using smaller doses for a longer period of time.

As for the limitations of the present study, one is the lack of additional verification of participants' compliance with the no-consumption instructions. Subjects' urinary or plasma levels of THC metabolites (THC-COOH) were not examined to confirm cannabis use status. Another limitation is the correlative nature of the study, which does not preclude causal contributions from possible self-selection factors, such as a predisposition for low striatal DA production that seduces people to use cannabis. It may also be suspected that significantly more nicotine smokers in the chronic cannabis condition might have contributed to the difference in the observed EBR between groups. However, not only did the critical effect survive the input of nicotine use as covariate but research also indicates that the long-term effect of nicotine on DA is facilitatory rather than inhibitory (Quik et al., 2006). This suggests that, if anything, the observed reduction in EBR provides a rather conservative estimate of the association between cannabis use and striatal DA levels.

To conclude, the results of the present study point to less efficient striatal dopaminergic functioning in chronic cannabis users. This finding seems crucial in understanding the suspected psychotic effects of long-term cannabis use and throws some doubt on the claim that cannabis-induced psychosis results from the combination of increased striatal and reduced prefrontal DA levels (Kuepper et al., 2010). Additionally, the fact that cannabis has an

indirect effect on DA implies caution in predictions of DA-related disorders due to chronic cannabis use. As a result of dopaminergic neurons not being impaired by cannabinoids, long-term consequences of cannabis exposure may be less severe than in the case of drugs directly damaging dopaminergic cells, as occurs with cocaine use (for a discussion, see: Colzato et al., 2008). More research is required in order to identify the neurophysiological and cognitive effects of continuous marijuana use, which are likely to be more subtle than those of other recreational drugs.

Materials and Methods

Participants

Fifty-three healthy adults served as participants: 28 chronic cannabis users and 25 non-user controls. Participants received either course credit or financial reward. The sample was obtained from the city of Leiden using local advertisement, posts on community bulletin boards, and leaflets distributed in Leiden "coffee shops" (in which Dutch law permits selling/serving soft drugs to customers). Subjects were informed that they will participate in a study on the cognitive and neural effects of cannabis.

Following Colzato and Hommel (2008), the inclusion criterion for cannabis users was a weekly consumption of at least four joints for a minimum of 2 years. The exclusion criteria were: (1) current or previous regular use of other drugs except for cannabis (regular use defined as having used a drug more than three times in a lifetime), (2) abuse of alcohol (more than 14 units per week), (3) history or presence of an Axis 1 psychiatric disorder (DSM-IV; assessed with the use of the Mini International Neuropsychiatric Interview; M.I.N.I. [Lecrubier et al., 1997]), (4) clinically significant medical disease, and (5) use of psychotropic medication. Non-user controls were required to meet the same criteria, with the exception that they could not report current or previous cannabis use. Additionally, participants were not permitted to consume caffeine, chocolate, or alcohol 12 hours before the experimental session, or to use nicotine 2 hours before the study. It was also not allowed to use cannabis on the day of study. However, cannabis use on the previous day was accepted in order to minimize the impact of possible withdrawal effects of addicted chronic users. Within the study sample, two participants were rescheduled for another day due to non-compliance with the consumption avoidance requirements.

Three individuals were excluded from the group of chronic users because of meeting the criteria for a psychiatric disorder.

Both groups were matched for age, gender, race (92% Caucasian, 8% Turkish), and IQ (measured by Raven's Standard Progressive Matrices; SPM [23]). The demographic and cannabis use statistics are presented in Tables 1 and 2, respectively. Additionally, in Table 1 the results of t-tests are presented to provide a comparison of demographic group characteristics. Written informed consent was acquired from all participants after the nature of the study had been explained to them. The protocol and compensation for participants were approved by the institutional review board (Leiden University, Institute for Psychological Research).

Table 1 *Demographic data.*

	Non-user controls	Chronic cannabis users	Significance level
N (M : F)	25 (13 : 12)	25 (19 : 6)	n.s.
Age (years)	21.7 (3.8)	23.9 (4.4)	n.s.
Race	23 C : 2 T	23 C : 2 T	n.s.
Raven IQ	124.4 (5.6)	124.2 (7.6)	n.s.
Alcohol use	3.1 (2.4)	3.9 (2.8)	n.s.
Nicotine use	4 S : 21 NS	21 S : 4 NS	**

Standard deviation in parentheses; n.s.: non-significant difference; Race: C – Caucasian, T – Turkish; Raven IQ: measured by Raven's Standard Progressive Matrices; Alcohol use: consumption of units per week; Nicotine use: S – smoker, NS – non-smoker.
**$p < 0.01$.

Table 2 *Self-reported cannabis use.*

Sample	Mean (SD)
Years of exposure	5.4 (4.4)
Age of onset	18.4 (2.9)
Monthly regular use	62.5 (45.7)
Peak use in a month	131.8 (81.6)
Lifetime consumption	4895 (7409.4)

Standard deviation in parentheses; Monthly regular, monthly peak cannabis use and lifetime consumption: consumption of joints.

Procedure and Design

Spontaneous EBR was recorded using a BioSemi ActiveTwo system (BioSemi Inc., Amsterdam, The Netherlands). The recording took place with two horizontal (one left, one right) and two vertical (one upper, one lower of right eye) Ag-AgCl electrodes. A vertical electrooculogram (EOG), which records the voltage difference between two electrodes placed above and below the left eye, was used to detect eye blinks. A horizontal EOG, which records the voltage difference between electrodes placed lateral to the external canthi, was used to measure horizontal eye movements in order to provide an online prevention of movement artifacts in the data. The EOG signals were digitized at 512 Hz. Data analysis was performed using Brain Vision Analyzer (Brain Products™ GmbH, Munich, Germany; http://www.brainproducts.com/products/analyzer/index_analyzer.html) with a high-pass filter of 1 Hz applied offline. Eye blinks were semi-automatically detected using the built-in Gratton and Coles (Gratton et al., 1983) algorithm. Recordings did not take place after 5 p.m. due to spontaneous EBR being stable during daytime, but increasing in the evening (around 8:30 p.m. [Barbato et al., 2000]). Participants were comfortably sitting in front of a blank poster with a cross in the center, located about 1 m from the subject. Participants were alone in the room and asked to look at the cross in a relaxed state. The recording lasted 6 minutes. Individual EBR was calculated by dividing the total number of eye blinks during the 6-minute measurement interval by six.

Acknowledgments

We thank Kees Frans for his invaluable assistance in recruiting and testing the participants and collecting the data.

3

The acute impact of cannabis on creativity*

* This chapter is based on:

Kowal MA, Hazekamp A, Colzato LS, van Steenbergen H, van der Wee NJA, Durieux J, Manai M, Hommel B (2015a) Cannabis and creativity: highly potent cannabis impairs divergent thinking in regular cannabis users. Psychopharmacology 232:1123-1134. DOI: 10.1007/s00213-014-3749-1

Abstract

Rationale Cannabis users often claim that cannabis has the potential to enhance their creativity. Research suggests that aspects of creative performance might be improved when intoxicated with cannabis; however, the evidence is not conclusive.

Objective The aim of this study was to investigate the acute effects of cannabis on creativity.

Methods We examined the effects of administering a low (5.5 mg THC) or high (22 mg THC) dose of vaporized cannabis vs. placebo on creativity tasks tapping into divergent (Alternate Uses Task) and convergent (Remote Associates Task) thinking, in a population of regular cannabis users. The study used a randomized, double-blind, between-groups design.

Results Participants in the high dose group (n = 18) displayed significantly worse performance on the divergent thinking task than individuals in both the low dose (n = 18) and placebo (n = 18) groups did.

Conclusions The findings suggest that cannabis with low potency does not have any impact on creativity while highly potent cannabis actually *impairs* divergent thinking.

Keywords

cannabis, creativity, divergent thinking, convergent thinking

Introduction

Anecdotal evidence suggests that cannabis intoxication enhances human creativity. In line with that, Steve Jobs, an undeniably creative mind, once stated: "The best way I could describe the effect of the marijuana and hashish is that it would make me relaxed and creative". Other regular users claim that cannabis induces a state in which they experience unusual and original thoughts (Tart, 1970). In a more recent review, over 50% of users reported heightened creativity during cannabis intoxication (Green et al., 2003). This widespread perception of cannabis as a creativity-enhancer makes it important to verify whether cannabis actually induces these supposed effects. Delta-9-tetrahydrocannabinol (THC), the main psychoactive compound present in the *Cannabis sativa* plant, has been found to reduce inhibitory control (McDonald et al., 2003) and stimulate striatal dopamine (DA) release (Bossong et al., 2009; Kuepper et al., 2013). These features of THC intoxication, in turn, are expected to play a role in particular aspects of creative thinking (Akbari Chermahini et al., 2010; Hommel, 2012). On the other hand, THC has been linked to the emergence of psychotic symptoms due to acute administration (D'Souza et al., 2004), as well as in the long-term (Kuepper et al., 2010). As a result, the possible beneficial effects of using cannabis, if any, might not outweigh the potential risks associated with its abuse.

The concept of creativity is not very well defined and there is no agreement on one particular measure of how to assess it. While some authors consider the concept to refer to the product of creative activities, others take it to reflect the personality of the product's creator (for an overview, see: Runco, 2007). To circumvent these difficulties, we restricted our analyses to two well-established creative processes, and the respective classical assessment methods: divergent and convergent thinking (Guilford, 1967). Divergent thinking takes place when people try to find as many solutions to a loosely defined problem as possible—a process often referred to as "brainstorming". It is often assessed by means of Guilford's (1967) Alternate Uses Task (AUT), which requires individuals to generate as many as possible uses for a common household item (such as a pen or book) as they can think of (e.g., reading it, using it as a doorstop, etc.). In contrast, convergent thinking takes place when trying to find the one possible solution to a very well defined problem. This process is often assessed by means of Mednick's (1962) Remote Associates Task (RAT), in which people are presented with three supposedly unrelated concepts (e.g., "time", "hair", "stretch") and are requested to identify the one concept that can

be related to all three of them ("long"). Research indicates that performance in AUT and RAT is not (strongly) correlated (Akbari Chermahini and Hommel, 2010; Akbari Chermahini et al., 2012). Moreover, there is evidence that the two types of creative thinking are differently related to subcortical DA levels: while divergent thinking performance relates to markers of DA levels in the form of an inverted U-shape, convergent thinking performance displays a linear, negative correlation with DA markers (Akbari Chermahini and Hommel, 2010). In addition, this dissociation of human creativity seems to correspond to the Dual Pathway to Creativity model (De Dreu et al., 2008; Nijstad et al., 2010) suggesting that creative performance emerges from the balance between cognitive flexibility and cognitive persistence—two dissociable cognitive control functions (De Dreu et al., 2012).

With regard to the neural effects of THC, the link between creative thinking and DA appears to be particularly interesting. Administration of THC has been shown to indirectly induce DA release in the striatum (Bossong et al., 2009; Kuepper et al., 2013) and there is evidence that its chronic application can lead to dopaminergic hypoactivity in the long-term, especially if the onset of cannabis use is at a young age (Hoffman et al., 2003; Urban et al., 2012; Bloomfield et al., 2014). As divergent thinking performance is expected to be optimal with medium subcortical DA levels (Akbari Chermahini and Hommel, 2010), one may suspect that THC can have a beneficial effect on this creative process, particularly in individuals with low dopaminergic functioning. This assumption is further supported by the fact that the reduction in inhibitory control, as observed in response to stimulation by pure THC (McDonald et al., 2003) and cannabis (Ramaekers et al., 2006; Ramaekers et al., 2009), has been related to dopaminergic functioning as well (Mink, 1996). Reduced inhibitory control can be considered to reflect a cognitive control state with weak top-down guidance. Such a state should affect convergent and divergent thinking differently (Hommel, 2012). As pointed out by Bogacz (2007), human decision-making and the retrieval of possible alternatives can be considered a process that emerges from the interaction of top-down guidance and low-level competition between alternatives. If so, convergent thinking, with its many top-down constraints targeting one single solution, would seem to require a control state that provides strong top-down guidance and strong local competition. In contrast, divergent thinking, with its loosely defined problem and its many solutions, seems to require a control state that provides weak top-down guidance and only little local competition (Hommel 2012). To the degree that THC indeed induces a control state with weak top-down guidance and

local competition, it might thus be expected to improve divergent thinking, interfere with convergent thinking, or both (Hommel, 2012; Colzato et al., 2012).

Unfortunately, the available research on the link between cannabis and creativity allows only for partial verification of these expectations. With respect to divergent thinking, one study showed that subjects intoxicated with joints (cannabis cigarettes) containing a low dose of THC (3 mg in total) displayed significantly enhanced performance on two divergent production tasks, compared to a group that received a higher THC dose (6 mg in total; Weckowicz et al., 1975). Curran et al. (2002) showed that, as compared to placebo, oral THC (7.5 and 15 mg) dose-dependently improved verbal fluency—an important aspect of divergent thinking (Guilford, 1967), at least as assessed by the AUT. Improved verbal fluency performance was also found in a naturalistic study that showed the beneficial effect of smoked cannabis (10% THC on average) on divergent thinking to be restricted to users low in trait creativity (i.e., individuals that obtained a low score on a self-assessment questionnaire about achievements in different creative domains; Schafer et al., 2012). In addition to fluency, cannabis administration (joints containing 19 mg of THC) has also been shown to increase the number of original responses on a test of associative processes, in comparison to placebo (Block et al., 1992). In contrast, Tinklenberg et al. (1978) did not observe any improvement in performance during the Torrance Tests of Creative Thinking (TTCT; Torrance, 1966), which is often assumed to tap into divergent thinking, after oral consumption of THC (a biscuit containing 0.3 mg/kg body weight of THC). Another study found decreased TTCT scores for fluency, flexibility, and elaboration after smoking a cannabis joint (containing 10 mg of THC) in regular cannabis users but not in first-time users (Bourassa and Vaugeois, 2001). In summary, the methodological differences between the various studies aside, many but not all findings suggest that THC may induce a cognitive control state with weak top-down guidance, thus efficiently decreasing the competition between cognitive representations and enhancing divergent thinking (Hommel 2012; Colzato et al., 2012).

For convergent thinking, the evidence is even more limited. Weckowicz et al. (1975) observed a trend towards less efficient convergent thinking tasks after smoking joints containing a low dose of THC (3 mg in total) or a higher dose (6 mg in total), in comparison to both a placebo and a pure control group. However, the same study also found impaired convergent thinking but only for the high dose condition. The most recent investigation found potentially

detrimental effects of smoking cannabis (10% THC on average) on RAT performance in a group of cannabis users assumed to be high in trait creativity (Schafer et al., 2012). Although the naturalistic approach of this study makes it difficult to account for specific dose-related differences, the results of the research of both Schafer et al. (2012) and Weckowicz et al. (1975) suggest that THC can disrupt the process of searching and converging on a single solution to a problem.

A number of the observed inconsistencies between studies might be due to differences with respect to THC dosage and method of administration, which, in turn, affects the bioavailability and the onset of action of the compound (Hazekamp et al., 2006). Moreover, an individual's history of cannabis use needs to be identified before cognitive changes in response to THC can be predicted. Administration of joints (containing up to 39 mg of THC) to regular cannabis users has been found to produce no accuracy impairments on a test battery assessing several cognitive functions (Hart et al., 2001) and, more specifically, on tasks related to episodic and working memory (Hart et al., 2010). Furthermore, after smoking a cannabis joint (containing 500 μg/kg body weight THC), chronic users did not display any behavioral deficiencies on tasks assessing tracking performance and divided attention (Ramaekers et al., 2009), or changes in an event-related potential (ERP) reflecting early attentional processes (Theunissen et al., 2012), compared to infrequent users. In addition, regular cannabis users were shown to display reduced sensitivity to the psychotomimetic effects of THC (administered as an intravenous dose of up to 5 mg; D'Souza et al., 2008). In contrast, inhibitory control has been found to be similarly impaired among both occasional and chronic users when intoxicated with cannabis (Ramaekers et al., 2009).

Accordingly, since research points to reduced cannabinoid receptor type 1 (CB_1) density in the brains of regular cannabis users (Hirvonen et al., 2012), one may suspect that the tolerance of chronic users to some of the detrimental effects of THC is, to some extent, related to their dopaminergic functioning. Specifically, due to the concentration of CB_1 receptors at gamma-aminobutyric acid (GABA) and glutamate neurons, CB_1 receptor downregulation can influence the activity of these neurotransmitters (Hoffman et al., 2003). Because DA neurons are frequently co-localized with GABAergic and glutamatergic terminals, the dopaminergic deficiencies observed in chronic cannabis users may be explained by lasting, maladaptive modulation of DA by GABA and glutamate (Fattore et al., 2010; Fernández-Ruiz et al., 2010). If so, keeping in mind the inverted U-shaped relationship between subcortical DA

levels and divergent thinking performance (Akbari Chermahini and Hommel, 2010) and the effect of THC on striatal DA release (Bossong et al., 2009; Kuepper et al., 2013), it may be expected that individuals with a relatively low level of dopaminergic functioning, such as regular cannabis users, are more likely to demonstrate enhanced performance on a divergent thinking task, provided that the THC dose is not excessively high. In contrast, in a population without long-term dopaminergic imbalances, such as healthy drug-naïve individuals, even a reasonably low dose of THC could stimulate DA production to a level that exceeds the threshold for optimal performance. In the case of convergent thinking performance, which is best with low subcortical DA levels (Akbari Chermahini and Hommel, 2010), it may be predicted that it will deteriorate in response to THC, irrespective of the dose and cannabis use history of the individual.

In order to examine these possibilities, we investigated the effect of two different doses of vaporized cannabis (containing 5.5 or 22 mg of THC; see section *Study drugs*) and placebo on convergent and divergent thinking in a sample of chronic cannabis users, using a between-groups design. On the basis of the assumption that a low dose of cannabis can remove potential impairments caused by regular use (Weckowicz et al., 1975; Kelleher et al., 2004), we expected that participants intoxicated with a low dose of cannabis should display higher scores on a divergent thinking task than those receiving placebo would. Conversely, we predicted impairment of performance in the high dose condition, in contrast to the low dose and placebo conditions. In the case of convergent thinking, we expected that both doses of cannabis should impair this process, compared to placebo. In addition, since divergent thinking performance has been found to be related to an individual's mood (Zenasni and Lubart, 2011), we assessed perceived mood as a possible modulating factor.

Materials and Methods

The current study was part of a larger study which involved additional tasks and measurements.

Participants

Power analysis was performed to assess the approximate number of subjects required for detecting medium ($d = 0.5$) or large effect sizes ($d = 0.8$).

Consequently, with an expected sample size of 60, three conditions, and a set alpha of 0.05, the power to detect main effects with a medium or large effect size for a between-groups ANOVA is 0.679 and 0.979, respectively. Calculations were made using the analysis program fpower (Friendly 2014).

Fifty-nine healthy regular cannabis users (52 males and seven females) participated in the study in exchange for a small financial compensation. Subjects were recruited through advertisements on the internet, on community bulletin boards, and in coffee shops (outlets in which Dutch law permits the sale of small quantities of cannabis to consumers) and by word of mouth. Detailed demographic and substance use information is presented in Table 1. Written informed consent was obtained from all participants after a complete explanation of the nature of the study. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center.

The participants were randomly assigned to one out of three experimental conditions: placebo, 5.5 mg or 22 mg of THC. The groups were comparable in terms of age, substance use characteristics, and IQ test score. All subjects were required to be regular users (use cannabis at least four times a week, for a minimum of 2 years) and to be native Dutch speakers. The exclusion criteria were: (1) history or presence of an axis I psychiatric disorder (DSM-IV; assessed with the use of the Mini International Neuropsychiatric Interview; M.I.N.I: Lecrubier et al., 1997); (2) clinically significant medical disease; (3) use of psychotropic medication; (4) current or previous regular use of other drugs except cannabis (regular use defined as having used a drug more than four times in a lifetime); (5) abuse of alcohol (more than 14 units a week). Compliance with the inclusion and exclusion criteria was assessed by means of self-report. Additionally, subjects were asked to refrain from caffeine, chocolate, and alcohol 12 hours before the experimental session and not to use nicotine 2 hours before the study. It was also not allowed to use cannabis within 2 days before the experiment. Participants' compliance with these criteria was evaluated by means of a personal interview and the use of a saliva drug test, which detected the recent use of cannabis, morphine, or cocaine (Oral-View™ Saliva Multi-Drug of Abuse Test; Alfa Scientific Designs Inc., Poway, CA, U.S.A.).

From the initial sample of 59 subjects, two male participants withdrew from the study before completing the two creativity tasks—one stated personal issues, while the other did not provide any explanation. Another subject experienced anxiety before cannabis administration and had to abort the experiment. In the case of adverse events related to drug administration, one

participant reported anxiety, combined with fatigue and nausea, which prevented him from completing the tasks. Moreover, one female subject was excluded from the analysis due to lack of compliance to task requirements (i.e., she refused to complete the tasks due to not liking their nature). This left 54 subjects for the final analysis (48 males and six females), except for the convergent thinking task (RAT). In this case, one male participant (in the 22 mg THC condition) requested to abort the study due to personal reasons before being able to complete the task, which left only 53 data sets for the RAT analysis.

Study drugs

The active drug substance consisted of the dried, milled, and homogenized flowers of the plant *Cannabis sativa* (variety 'Bedrocan'®; 19% THC). It was obtained from Bedrocan BV (Veendam, The Netherlands) where it was cultivated under standardized conditions according to the requirements of Good Agricultural Practice (GAP). The placebo (variety 'Bedrocan'®; <0.5% THC) used in the study had a moisture content and terpenoid profile (providing the typical smell and taste of cannabis) identical to the active drug. Study medication was prepared by ACE Pharmaceuticals BV (Zeewolde, The Netherlands). For each individual dose, exact amounts of active cannabis and placebo were mixed so that each dose was equal to 250 mg total weight but with varying concentrations of THC (placebo/5.5 mg/22 mg THC). Study medication was stored in a refrigerator (2–8°C) in triple-layer laminated foil pouches (Lamigrip). Shelf life stability under these conditions was determined to be at least 1 year.

On the study day, each subject received a randomized single dose of cannabis by means of a Volcano® vaporizer (Storz&Bickel GmbH, Tüttlingen, Germany)—a reliable and safe method of intrapulmonary administration of THC (Hazekamp et al., 2006; Zuurman et al., 2008). Cannabis was vaporized at a temperature of 230°C into a standard Volcano balloon as supplied with the vaporizer. For blinding purposes, the Volcano balloon was covered with a non-transparent plastic bag so that no differences in the density of the vapor were visible between dosages.

When administering THC by means of vaporizing, it should be taken into account that only part of the dose present in the plant material is vaporized into the balloon (Hazekamp et al., 2006), and that a portion of the THC inhaled from the balloon is not absorbed by the lungs but is exhaled again (Zuurman et al., 2008). Therefore, in order to achieve an absorbed dose of

approx. 2- and 8 mg THC, we loaded the Volcano vaporizer with 5.5 and 22 mg of THC, respectively. Moreover, since the THC delivery of the Volcano vaporizer and cannabis joints is comparable (Abrams et al., 2007), the loaded vs. absorbed dose distinction can be applied to smoked cannabis as well.

During administration, subjects were instructed to inhale deeply and hold their breath for 10 seconds after each inhalation. They were not allowed to speak during the inhalation period and were required to empty the balloon within 5 minutes. Subjects had the opportunity to practice the inhalation procedure using an empty balloon before cannabis administration.

Shortened Raven's Standard Progressive Matrices (SPM; measure of intelligence)

Individual IQ test scores were determined by means of a reasoning-based intelligence test (Raven et al., 1988). Each item of this test consists of a pattern or sequence of a diagrammatic puzzle with one piece missing, the task being to complete the pattern or sequence by choosing the correct missing piece from a list of options. The items get more difficult as the test taker proceeds through the test. The SPM test assesses the individual's ability to create perceptual relations and to reason by analogy independent of language and formal schooling. The version of the test used in the study consisted of 14 items.

Alternate Uses Task (AUT; divergent thinking)

In this task (Guilford, 1967) participants were asked to list as many possible uses for two common household items (i.e., pen, shoe) as they could. The scoring had four components: *Fluency* (the total of all responses); *Flexibility* (the number of different categories used; e.g., "household uses"); *Originality* (where each response was compared to the responses from the other subjects, responses given by only 5% of the participants being counted as unusual [1 point] and responses given by only 1% as unique [2 points]); and *Elaboration* (referring to the amount of detail; e.g., while a book used as “a doorstop” would count 0, “a doorstop to prevent a door slamming shut in a strong wind” would count 2: 1 point for explanation of door slamming and 1 point for additional detail about the wind). Of these four criteria, the component *flexibility* has been found to be the theoretically most transparent and the empirically most consistent and reliable score (Akbari Chermahini and Hommel, 2010).

Remote Associates Task (RAT; convergent thinking)

In this task (developed by Mednick [1962]), participants were presented with three unrelated words (e.g., time, hair and stretch) and asked to find a common associate (long). The test consisted of 14 items, which were taken from Akbari Chermahini et al.'s (2012) Dutch version of the RAT.

Affect grid (subjective measure of mood)

As in Colzato et al. (2013), the current mood of participants was assessed by means of a 9 × 9, Pleasure × Arousal grid (Russell et al., 1989).

Visual analogue scales (VAS; subjective measure of drug effects)

The subjective effects of cannabis were assessed by means of three scales (horizontal 100-mm lines, the left pole labeled "not at all" and the right "extremely") referring to "(feeling) High", "Good drug effect", and "Bad drug effect". Participants were to mark a point at the continuous line to indicate their experience.

Design and procedure

The study used a randomized, double-blind, placebo-controlled, between-groups (placebo vs. 5.5 mg vs. 22 mg THC) design. All participants were tested individually and the order of the two creativity tasks—AUT and RAT—was counterbalanced. Upon arrival, the subjects were asked to complete the SPM test within 10 minutes. Afterwards, the study drug was administered. Six minutes after cannabis administration, participants were required to indicate the subjective effects of the drugs by means of the VAS. This assessment of the effects of the drugs was then repeated twice—before and after the completion of the two creativity tasks (35 and 60 minutes after administration). Participants were provided with both the AUT and RAT in printed form (in the time window between 35 and 60 minutes after administration) and had 10 minutes to complete each task. In addition, in order to evaluate the subjective perception of mood, subjects were required to rate their mood on the Affect grid after the completion of each creativity task (at 48 and 60 minutes after administration).

Statistical analysis

Scores from mood assessments and VAS, together with the five measures from the two creativity tasks (fluency, flexibility, originality, and elaboration scores from the AUT; the number of correct items from the RAT)

were calculated for each subject. The results of the AUT were rated by two independent readers, blinded to the conditions (Cronbach's alpha = 1.00 [fluency]; 0.87 [flexibility]; 0.94 [originality]; 0.9 [elaboration]). The final scores were the means of both ratings. All measures were analyzed separately. In the case of the AUT, RAT, and IQ test scores, age, and substance use data, between-groups ANOVAs were run with condition (placebo vs. 5.5 mg vs. 22 mg THC) as between-groups factor. Data regarding sex was analyzed with the use of a Pearson's chi-squared test. Mood and VAS scores were analyzed by means of repeated-measures ANOVAs with time after cannabis administration (48 vs. 60 minutes for mood; 6 vs. 35 vs. 60 minutes for VAS) as a within-subjects factor and condition as a between-groups factor. *Post-hoc* multiple comparison t-tests were applied with Bonferroni correction. A significance level of $p < 0.05$ was adopted for all tests.

Results

Demographic and substance use data

No significant main effects of condition were found in the case of age ($F(2, 51) = 0.74$, $p = 0.482$), IQ test score ($F(2, 51) = 0.159$, $p = 0.854$), monthly cannabis use ($F(2, 51) = 0.453$, $p = 0.639$), years of cannabis exposure ($F(2, 51) = 1.433$, $p = 0.248$), monthly alcohol use ($F(2, 51) = 0.855$, $p = 0.431$), years of alcohol exposure ($F(2, 51) = 3.027$, $p = 0.057$), monthly nicotine use ($F(2, 51) = 1.231$, $p = 0.3$), and years of nicotine exposure ($F(2, 51) = 0.383$, $p = 0.684$). However, the experimental conditions significantly differed by sex ($\chi^2(2, N = 54) = 7.875$, $p = 0.019$); see Table 1.

Creativity tasks

Overall task performance in the AUT and RAT was comparable to that in studies without pharmacological interventions (e.g., Akbari Chermahini and Hommel 2010); see Figure 1 and Table 2.

Divergent thinking

Significant main effects of condition were found on fluency ($F(2, 51) = 7.378$, $p = 0.002$), flexibility ($F(2, 51) = 7.708$, $p = 0.001$), and originality ($F(2, 51) = 8.952$, $p < 0.001$), but not on elaboration ($p > 0.05$).

As expected, *post-hoc* multiple comparisons revealed that participants in the 22 mg THC condition showed significantly reduced scores from those of

the participants in the placebo and 5.5 mg THC groups, respectively, for fluency ($t(34) = 3.072$, $p = 0.01$; $t(34) = 3.582$, $p = 0.003$), flexibility ($t(34) = 3.061$, $p = 0.011$; $t(34) = 3.367$, $p = 0.002$) and originality ($t(34) = 2.584$, $p = 0.045$; $t(34) = 4.021$, $p < 0.001$). However, contrary to expectations, subjects in the 5.5 mg THC condition did not display any significant increases from those receiving placebo, on any of the AUT components ($p > 0.05$).

Moreover, in order to test whether sex differences had an impact on the observed results and match the groups for sex, we repeated the analysis after the exclusion of all female subjects. Significant main effects were retained for fluency ($F(2, 45) = 5.774$, $p = 0.006$), flexibility ($F(2, 45) = 6.325$, $p = 0.004$), and originality ($F(2, 45) = 7.641$, $p = 0.001$).

Convergent thinking

Contrary to expectations, there was no main effect of condition on the number of correct items from the RAT ($p > 0.05$).

Table 1 *Demographic and substance use data for each experimental group.*

	Placebo	5.5 mg THC	22 mg THC	Significance level
N **(Male : Female)**	18 (18 : 0)	18 (17 : 1)	18 (13 : 5)	$p = 0.019$
Age	21.1 (2.4)	21.1 (2.1)	22 (2.5)	n.s.
IQ test score	7.8 (2.6)	7.3 (2.7)	7.4 (2.3)	n.s.
Monthly cannabis use	42.8 (31.3)	51.3 (52.6)	39.3 (27.8)	n.s.
Years of cannabis exposure	6 (3.1)	4.8 (1.9)	6.2 (2.6)	n.s.
Monthly alcohol use	26.2 (17.8)	23.7 (19.8)	18.8 (13.5)	n.s.
Years of alcohol exposure	5.3 (2.6)	4.8 (2.5)	6.9 (2.7)	n.s.
Monthly nicotine use	214.4 (207.7)	121.3 (140)	156 (185.3)	n.s.
Years of nicotine exposure	4.6 (3.8)	3.5 (4.2)	4.3 (4)	n.s.

Standard deviations in parentheses; n.s.: non-significant difference; Age: reported in years; IQ test score: measured by a shortened version of Raven's Standard Progressive Matrices; Monthly cannabis use: consumption of cannabis cigarettes (joints); Monthly alcohol use: consumption of alcohol units; Monthly nicotine use: consumption of cigarettes.

Table 2 *Means, SD, and ANOVA results for the four components of the Alternate Uses Task (AUT: fluency, flexibility, originality, elaboration), and the number of correct items from the Remote Associates Task (RAT), for each experimental group.*

	Placebo	5.5 mg THC	22 mg THC	*F*	*p*	η^2_p	*MSE*
AUT							
*Fluency	29.2 (9.5)	30.6 (9.2)	19.6 (9)	7.378	0.002	0.224	86.615
*Flexibility	22.3 (4.9)	23.6 (6.2)	16 (7.2)	7.708	0.001	0.232	38.683
*Originality	21.2 (8.4)	27.5 (11.5)	14.1 (8.1)	8.952	<0.001	0.26	90.63
Elaboration	2.5 (2.8)	1.2 (1.6)	1.2 (1.6)	2.152	0.127	0.078	4.552
RAT	4.8 (2.3)	4.5 (2.8)	4.9 (3.6)	0.116	0.891	0.005	8.904

*$p < 0.05$ (significant difference between 5.5- and 22 mg THC, and between placebo and 22 mg THC).

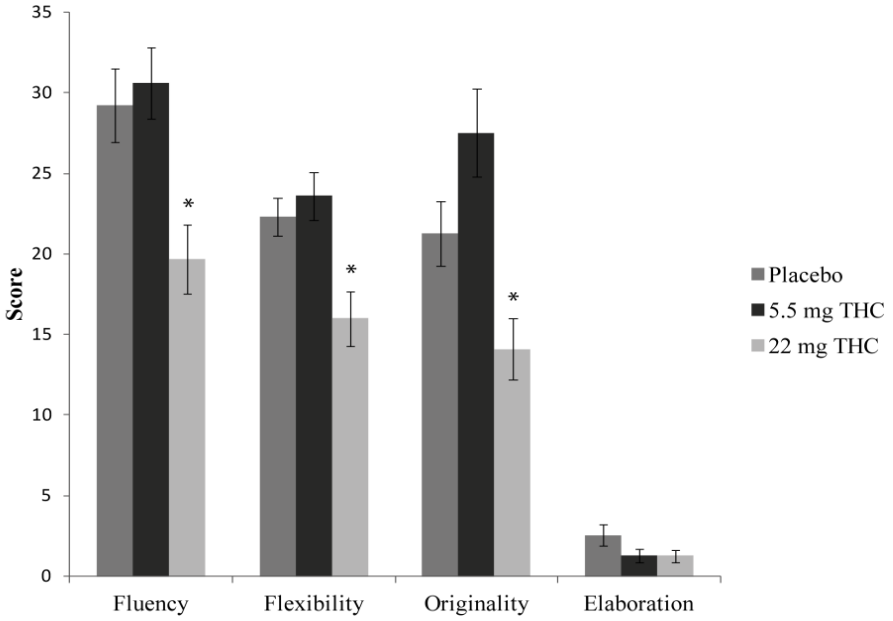

Figure 1 *Bar graphs showing mean scores for the four components of the Alternate Uses Task (AUT: fluency, flexibility, originality, elaboration) for each experimental group. The symbol (*) indicates a significant ($p < 0.05$) difference between the 5.5 mg and 22 mg THC conditions, and between the placebo and 22 mg THC conditions. Error bars represent SE of the mean.*

Subjective measures of drug effects and mood

Drug effects

Overall, only the rating of "high" showed a main effect of time after cannabis administration (with Huynh-Feldt correction; $F(1.862, 93.109) = 15.777$, $p < 0.001$). However, significant main effects of condition were found on all three scores: "high" ($F(2, 50) = 11.656$, $p < 0.001$), "good drug effect" ($F(2, 50) = 8.701$, $p = 0.001$), and "bad drug effect" ($F(2, 50) = 6.507$, $p = 0.003$). There were no significant interaction effects ($p > 0.05$).

Post-hoc multiple comparisons revealed that subjects in the placebo condition showed significantly lower ratings of "high" than the 5.5 mg ($t(34) = 2.95$, $p = 0.006$) and 22 mg THC groups ($t(34) = 4.49$, $p < 0.001$) did; see figure 2. Moreover, the ratings of "good drug effect" in the placebo condition were significantly lower than those in the 5.5 mg ($t(34) = 3.535$, $p < 0.001$) and 22 mg THC groups ($t(34) = 2.365$, $p = 0.023$); see figure 3. In the case of both "high"

and "good drug effect", no significant differences were found between the scores in the 5.5 mg and 22 mg THC groups ($p > 0.05$). Conversely, regarding the ratings of "bad drug effect", participants in the 22 mg THC condition demonstrated significantly increased scores from those in the placebo ($t(34) = 3.48$, $p = 0.006$) and 5.5 mg THC groups ($t(34) = 3.141$, $p = 0.012$); see figure 4. In addition, the ratings of "bad drug effect" did not significantly differ between the placebo and 5.5 mg THC conditions ($p > 0.05$).

Mood

There were no main effects of time after cannabis administration on the ratings of pleasure or arousal ($p > 0.05$). Moreover, mood ratings in the placebo (6.3 vs. 6.2 for pleasure; 5.1 vs. 5 for arousal), 5.5 mg (7.1 vs. 7 for pleasure; 5.5 vs. 5.2 for arousal), and 22 mg THC (6.1 vs. 6.4 for pleasure; 4.8 vs. 4.7 for arousal) conditions did not show significant main effects of condition on pleasure or arousal ($p > 0.05$). There were no significant interaction effects ($p > 0.05$).

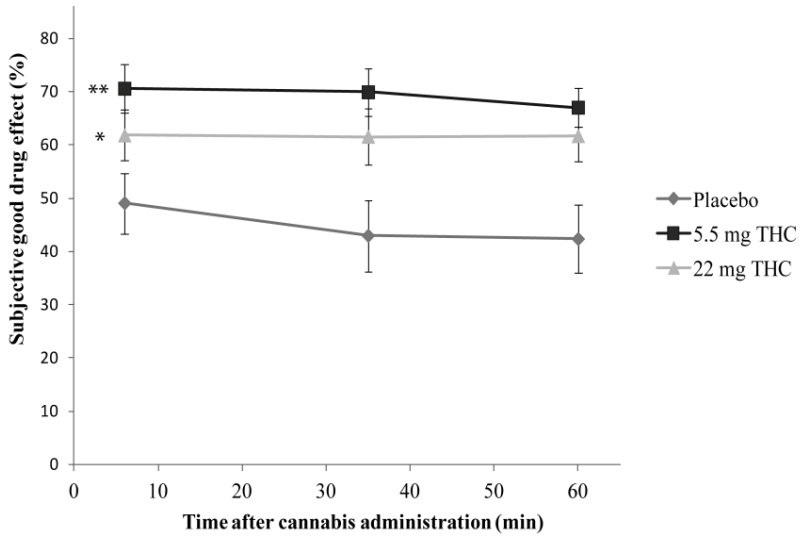

Figure 2 *Mean subjective high (rated as a percentage) experienced in each experimental group as a function of time after cannabis administration. Symbols indicate a significant ($p < 0.01$) difference between the 22 mg THC and placebo conditions (*), and between the 5.5 mg THC and placebo conditions (**). Error bars represent SE of the mean.*

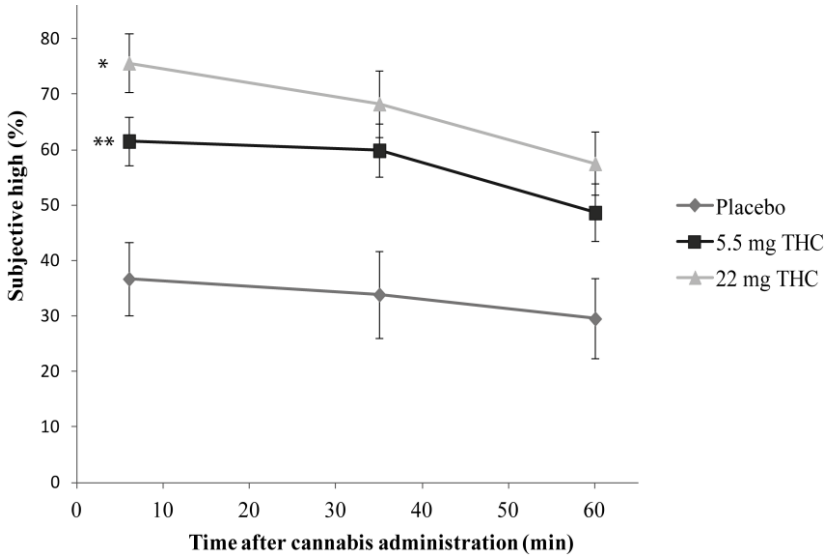

Figure 3 *Mean subjective good drug effect (rated as a percentage) experienced in each experimental group as a function of time after cannabis administration. Symbols indicate a significant ($p < 0.05$) difference between the 22 mg THC and placebo conditions (*), and between the 5.5 mg THC and placebo conditions (**). Error bars represent SE of the mean.*

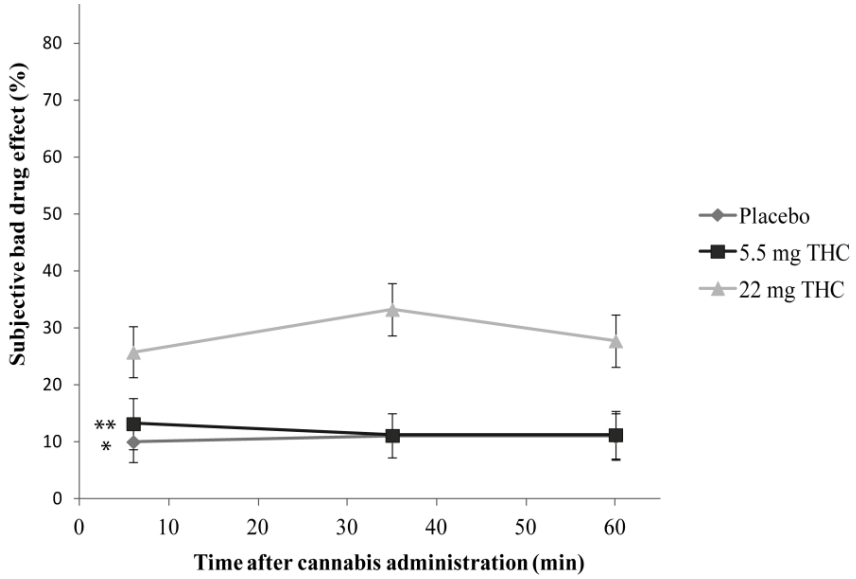

Figure 4 *Mean subjective bad drug effect (rated as a percentage) experienced in each experimental group as a function of time after cannabis administration. Symbols indicate a significant ($p < 0.05$) difference between the placebo and 22 mg THC conditions (*), and between the 5.5 mg and 22 mg THC conditions (**). Error bars represent SE of the mean.*

Discussion

Our findings demonstrate that a high dose of vaporized cannabis (22 mg THC) impairs divergent thinking in regular cannabis users, in comparison to a low dose (5.5 mg THC) and placebo cannabis preparation. This is reflected in the decreased scores for fluency, flexibility, and originality of responses of participants in the high dose condition. However, contrary to expectations, a low dose of cannabis did not enhance divergent thinking in chronic cannabis users: individuals in the low dose group did not significantly outperform subjects in the placebo group on any of the components of the AUT. Moreover, convergent thinking appears to be unaffected by either a low or high dose of cannabis, as condition had no impact on the numbers of correct RAT items.

Although the conclusions are limited by a between-groups design, the finding that administration of a high, but not low, dose of cannabis impairs divergent thinking performance of regular cannabis users may suggest that DA release in the striata of participants in the high dose condition (Bossong et al.,

2009; Kuepper et al., 2013) exceeded the threshold for optimal performance (Akbari Chermahini and Hommel, 2010). This is in line with neuroscientific considerations that point to a homeostatic function of DA in regulating the balance between opposing cognitive control states—flexibility and stability (Cools et al., 2009; Cools and D'Esposito, 2011). Flexibility refers to the ability to effectively switch between cognitive representations for the purpose of choosing the best alternatives, while the function of stability is to promote constancy of representations in spite of interference (Cools and D'Esposito, 2011). Consequently, keeping in mind the effect of cannabis on inhibition (Ramaekers et al., 2006; Ramaekers et al., 2009), it is safe to assume that individuals in the high dose condition experienced a reduction in inhibitory control after cannabis administration. Although this should promote a control state with weak top-down guidance allowing for flexible updating of information (Hommel, 2012; Colzato et al., 2012), supra-optimal levels of DA in the striatum have been found to stimulate flexibility to the point that it surpasses the threshold for optimal performance, inducing distractibility as a result (see: Cools and D'Esposito, 2011). Accordingly, it is possible that the observed impairment of divergent thinking in the high dose condition was the result of this process. Presumably, induction of a control state with weak top-down guidance is a necessary, but not sufficient, prerequisite for enhanced divergent thinking performance. Conversely, excessively potent cannabis may disturb the delicate balance between stability and flexibility by stimulating flexibility to its extreme, hence impairing divergent thinking.

In addition, from a more motivational perspective, it is possible that a high dose of cannabis induces the phenomenon of "ego-depletion" (i.e., exhausts the limited cognitive resources and motivation required for cognitive control operations; Baumeister et al., 1998; Inzlicht and Schmeichel, 2012). This seems probable taking into account the observation that participants in the high dose condition experienced more intense unpleasant subjective effects of cannabis than those in the low dose and placebo groups. In line with that, research points to anxiety, paranoia, delusions, and mental disorganization as frequent adverse effects of cannabis intoxication (Green et al., 2003; D'Souza et al., 2004). Therefore, the various undesirable forms of distraction induced by cannabis could have drained the control resources of individuals in the high dose condition. In other words, it is possible that the need to exert self-control over the adverse effects of cannabis leads to a reduction in motivation and available cognitive resources required for subsequent optimal divergent thinking performance (Inzlicht and Schmeichel, 2012).

In the low dose group, the lack of enhancement of divergent thinking does not provide support for the idea that a low dose of cannabis can eliminate cognitive impairments caused by regular use (Weckowicz et al., 1975; Kelleher et al., 2004). Nevertheless, since the performance of subjects in the low dose and placebo groups was comparable in the case of the AUT, it may be assumed that the lack of cannabis-induced cognitive deterioration in the low dose condition was indicative of the tolerance of regular cannabis users to the effects of the drug (Hart et al., 2001; Ramaekers et al., 2009; Hart et al., 2010; Theunissen et al., 2012). Furthermore, it is possible that the similar level of performance of both groups reflects their maximal potential for divergent thinking. Research indicates that placebo effects are able to stimulate subcortical DA release (Scott et al., 2007; Scott et al., 2008). Possibly, administration of a low dose of cannabis resulted in a dopaminergic response comparable to that in the placebo condition (Bossong et al., 2009; Kuepper et al., 2013). This seems plausible considering the fact that the placebo cannabis preparation used in the study was identical in terms of smell and taste to actual cannabis. As such, it had more potential to produce a placebo effect. In addition, the minimal amount of THC present in the placebo might have also affected DA release to some extent. Consequently, the subcortical DA levels of individuals in both the low dose and placebo conditions could have been within the range for optimal divergent thinking performance (Akbari Chermahini and Hommel, 2010).

Limitations

Although the most recent investigation into the link between cannabis and convergent thinking suggested a potentially detrimental effect of cannabis intoxication on this process (Schafer et al., 2012), our study failed to detect any impact on RAT performance. Perhaps our version of the task with 14 items was not sensitive enough to identify potential cannabis-induced impairments. Moreover, an important limitation is the between-groups design of the study. Consequently, it is possible that particular characteristics of the subject sample could have altered the effects of the drug. Specifically, the difference in sex between the conditions seems to be a likely candidate in this regard (Crane et al., 2013). In addition, research points to genetic predispositions like polymorphism of the CB_1 receptor gene (Ho et al., 2011; Stadelman et al., 2011), or the catechol-O-methyltransferase (COMT) gene (Schulz et al., 2012) as other factors which might modulate the cognitive effects of cannabis intoxication.

Another issue is related to the causal relation between the observed results and THC. In spite of the fact that application of cannabis, instead of pure THC, provides the benefit of a higher ecological validity of the study, the use of plant material could have influenced the findings. Specifically, terpenoids, which are the compounds responsible for the characteristic smell and taste of cannabis, have been shown to interact with cannabinoids to produce various synergistic effects (see: Russo, 2011). However, even if that was the case in our experiment, the terpenoid profile was comparable between the different doses, including the placebo cannabis preparation. Consequently, any potential terpenoid–cannabinoid interactions were controlled for. Unfortunately, the study lacked a measurement of THC blood plasma levels, which would allow for evaluating the relation between THC in the bloodstream and task performance. Furthermore, since the number of inhalations from the Volcano balloon and the duration of inhalations were not standardized, it is likely that this resulted in large differences in absorbed THC between subjects. In addition, the saliva test used in our experiment provided only an estimate of recent use. Possibly, the compliance of subjects with no-consumption criteria should instead be verified by examination of the urinary levels of THC metabolites (11-COOH-THC), which is capable of detecting intoxication over a longer period of time. Moreover, the lack of testing for alcohol intoxication can be considered another limitation in evaluating the compliance of participants with no-consumption criteria.

Conclusion

The findings indicate that administration of cannabis with a high THC content to regular cannabis users is detrimental for divergent thinking, while less potent cannabis does not seem to enhance this important component of creativity. The available evidence allows only for a speculation about the presence of these effects in a group of drug-naïve individuals, or occasional cannabis users. In any case, it can be claimed that the phenomenological experience of a person intoxicated with cannabis might not necessarily reflect his or her actual performance. In particular, the frequently reported feeling of heightened creativity could be an illusion. In other words, smoking a joint may not be the best choice when in need of breaking "writer's block", or overcoming other artistic inhibitions, and smoking several of them might actually be counter-productive.

4

The acute effects of cannabis on the neural correlates of error monitoring*

* This chapter is based on:

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Abstract

Cannabis has been suggested to impair the capacity to recognize discrepancies between expected and executed actions. However, there is a lack of conclusive evidence regarding the acute impact of cannabis on the neural correlates of error monitoring. In order to contribute to the available knowledge, we used a randomized, double-blind, between-groups design to investigate the impact of administration of a low (5.5 mg delta-9-tetrahydrocannabinol [THC]) or high (22 mg THC) dose of vaporized cannabis vs. placebo on the amplitudes of the error-related negativity (ERN) and error positivity (Pe) in the context of the Flanker task, in a group of frequent cannabis users (required to use cannabis minimally four times a week, for at least 2 years). Subjects in the high dose group (n = 18) demonstrated a significantly diminished ERN in comparison to the placebo condition (n = 19), whereas a reduced Pe amplitude was observed in both the high and low dose (n = 18) conditions, as compared to placebo. The results suggest that a high dose of cannabis may affect the neural correlates of both the conscious (late) and the initial automatic processes involved in error monitoring, while a low dose of cannabis might impact only the conscious (late) processing of errors.

Keywords: cannabis, THC, error monitoring, error-related negativity, error positivity

Introduction

Cannabis sativa is a plant which contains over 70 active constituents named cannabinoids (Schoedel and Harrison, 2012). Delta-9-tetrahydrocannabinol (THC), the main psychoactive cannabinoid present in the plant, has been found to evoke most of the subjective effects of marijuana (Grotenhermen, 2003). Around 20% of young people worldwide abuse the psychoactive effects of THC and other cannabinoids through regular use of the cannabis plant (Moore et al., 2007). This makes it important to understand whether and how cannabis intoxication affects human information processing. In the present study, we investigated the impact of cannabis on the monitoring of action errors, that is, on the recognition of discrepancies between expected and executed actions. To date, only one study has addressed the acute effects of cannabis on error monitoring (Spronk et al., 2011), while three other studies have considered the after-effects of chronic cannabis use (Hester et al., 2009; Harding et al., 2012; Fridberg et al., 2013). The present study aimed to contribute to the available knowledge by means of a between-subjects, double-blind, placebo-controlled design that compared the effects of two different doses of THC, in the form of herbal cannabis, on event-related potentials (ERPs) in a population of frequent cannabis users.

The monitoring of errors is an important element of cognitive control. It contributes to the fine-tuning of top-down control over information processing by signaling insufficient degrees of control to goal-related control systems (Botvinick et al., 2001). Interestingly for our purposes, the monitoring of errors can be assessed by means of electroencephalography (EEG). Specifically, a negative deflection can be noticed in the event-related potential (ERP) at around 50–100 ms after a person commits an error in a task—the so-called error-related negativity (Ne: Falkenstein et al., 1990; ERN: Gehring et al., 1993). The ERN has been established as a valid measure of error monitoring (Holroyd and Coles, 2002; Yeung et al., 2004; Ullsperger et al., 2014) and imaging research has identified the anterior cingulate cortex (ACC) as the most likely brain area responsible for generating the potential (Herrmann et al., 2004; Stemmer et al., 2004; Debener et al., 2005).

The ACC, aside of being an important relay station for cognitive control processes, is also a brain region that integrates cognitive and emotional information (Bush et al., 2000; Botvinick et al., 2001; Paus, 2001; Shackman et al., 2011). In line with that, it has been proposed that its activity is directly related to that of the mesencephalic dopamine (DA) system, by which the error signal is conveyed to the ACC (Holroyd and Coles, 2002). Considering the

neural effects of THC, the connection between error monitoring and DA seems to be especially interesting. Application of THC has been identified to indirectly stimulate DA production in the striatum (Bossong et al., 2009; Kuepper et al., 2013). Moreover, research indicates that chronic THC administration can result in long-term dopaminergic hypoactivity, particularly if the onset of cannabis use is at an early age (Hoffman et al., 2003; Urban et al., 2012; Bloomfield et al., 2014). Consequently, since error monitoring is assumed to depend on phasic changes in the tonic activity of the mesencephalic dopaminergic system (Holroyd and Coles, 2002), it seems likely that cannabis has an effect on this process.

In line with this DA account of the ERN, the only up-to-date study investigating the impact of acute administration of THC on error monitoring showed a reduced ERN in response to this cannabinoid (16 mg in total), compared to placebo (Spronk et al., 2011). Moreover, cannabis has been identified to alter the neural correlates of error monitoring in the long-term. Specifically, an ERP study showed an increased amplitude of the error positivity (Pe; i.e., a positive component which can be observed in the time interval between 200 and 500 ms after an erroneous response; Falkenstein et al., 2000) in a group of chronic cannabis users, compared to that in non-users (Fridberg et al., 2013). Although the Pe has not been studied as well as the ERN (Fridberg et al., 2013), evidence suggests that it represents a later stage of error processing, independent of the ERN (Falkenstein et al., 2000), and is linked to the conscious awareness of errors (Nieuwenhuis et al., 2001; Murphy et al., 2012). In the case of neuroimaging research, a decreased blood-oxygen level dependent (BOLD) signal to errors has been observed in the ACC and right insula of regular cannabis users, as compared to that in non-user controls (Hester et al., 2009). Furthermore, heightened demand for cognitive control has been associated with increased connectivity between the prefrontal (PFC) and occipitoparietal cortex (OP) in the brains of chronic users (Harding et al., 2012). Accordingly, the combined results of the different studies suggest that chronic cannabis use leads to both impaired error monitoring in these individuals and to possible development of a mechanism to compensate for the deterioration of the process of identification of errors in information processing. Specifically, compared to non-user controls, cannabis users recruit additional cortical activity in areas associated with cognitive control, or other brain regions not associated with this process (Tapert et al., 2007; Hester et al., 2009). In the case of the acute effects of cannabis, based on the single study by Spronk et al.

(2011), it can be assumed that error monitoring is impaired as a result of administration of THC.

Due to the scarcity of the data on this topic, it would be especially interesting to take into account different factors which can modulate the effect of administering THC on error monitoring. One such factor is the link between chronic and acute cannabis use. Specifically, the history of cannabis use of an individual has been shown to modulate the effects of cannabis intoxication. Chronic cannabis users smoking cannabis cigarettes (joints; containing maximally 39 mg of THC) have been shown to demonstrate no accuracy deficiencies on a number of tasks tapping into different cognitive functions (Hart et al., 2001) and, in particular, on episodic and working memory tests (Hart et al., 2010). In addition, compared to infrequent users, chronic users did not display any behavioral impairments on tasks evaluating tracking error and divided attention (Ramaekers et al., 2009) or changes in an ERP indicative of early attentional processes (Theunissen et al., 2012), following smoking of a cannabis joint (with 500 µg/kg body weight THC). Conversely, inhibitory control has been identified to be equally diminished among both chronic and occasional users due to cannabis administration (Ramaekers et al., 2009). In summary, it makes sense to assume that this specific cannabinoid tolerance of regular users is not limited to particular cognitive functions, but extends to the development of a compensatory mechanism for deficiencies in cognitive control (Harding et al., 2012; Fridberg et al., 2013). However, this compensation appears to have its limits due to impaired inhibitory control—a critical element in the top-down control over information processing (Botvinick et al., 2001).

Moreover, both the neurocognitive and the subjective effects of cannabis have been demonstrated to be highly dependent on the specific dose of THC administered (Hart et al., 2001; Ramaekers et al., 2006; Hart et al., 2010; D'Souza et al., 2012; Hunault et al., 2014). Consequently, when investigating the effect of cannabis on error monitoring, different results may be expected depending on the combination of the dose and history of cannabis use of the studied sample. For instance, a relatively low dose of THC may not produce visible changes in the error monitoring system of chronic cannabis users, while the compensatory mechanism may not be sufficient to prevent the impairments caused by a relatively high dose of THC.

In order to test these speculations, we examined the impact of two different doses of vaporized cannabis (5.5 mg or 22 mg of THC; see **Study drugs** section) and placebo on the amplitudes of the ERN and Pe. Moreover, we recruited only frequent cannabis users in our sample due to their partial

tolerance to the impairing effects of cannabis (Hart et al., 2001; Kelleher et al., 2004; D'Souza et al., 2008; Ramaekers et al., 2009; Hart et al., 2010; Theunissen et al., 2012). Accordingly, based on the characteristics of the studied sample and on the reported effects of a relatively high dose of THC on the ERN (16 mg in total; Spronk et al., 2011), we expected to observe a decreased ERN amplitude following administration of the high, but not low cannabis dose or placebo. Since no studies have investigated the acute effects of cannabis on the Pe, we could only speculate that it would be affected in a similar manner to the ERN. The ERN and Pe were assessed in the context of a modified version of the Flanker task (Eriksen and Eriksen, 1974). Since administration of cannabis to regular users does not usually lead to overt error impairments (Hart et al., 2001; Ramaekers et al., 2009; Hart et al., 2010), we did not expect to observe any effects at the behavioral level.

Experimental procedures

The current research was part of a larger study which included other tasks and measurements.

Participants

The program fpower (Friendly, 2014) was used to estimate the approximate number of participants needed for detecting medium (d = 0.5) or large effect sizes (d = 0.8). With an estimated sample size of 60, three conditions, and a set alpha of 0.05, the power to detect main effects with a medium or large effect size for a between-groups ANOVA was estimated at 0.679 and 0.979, respectively.

Sixty-one healthy frequent cannabis users (53 males and eight females) took part for a small financial compensation. Participants were recruited through advertisements on the internet, on community bulletin boards, and in coffee shops (outlets in which the sale of minor quantities of cannabis to consumers is allowed by Dutch law), and by word of mouth. Specific demographic and substance use information is displayed in Table 1. Written informed consent was obtained from all subjects after a complete explanation of the nature of the research. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center.

The subjects were assigned at random to one out of three experimental groups: placebo, 5.5 mg, or 22 mg THC. The conditions were comparable with

regard to sex, age, IQ test score, and substance use characteristics, except for years of alcohol exposure. All participants were requested to be frequent users (use cannabis minimally four times a week, for at least 2 years) and to be native Dutch speakers. The exclusion criteria were: (1) history or presence of an axis I psychiatric disorder (DSM-IV; assessed with the use of the Mini International Neuropsychiatric Interview; M.I.N.I: Lecrubier et al., 1997); (2) clinically significant medical disease; (3) use of psychotropic medication; (4) current or previous regular use of other drugs except cannabis (regular use defined as having used a drug more than four times in a lifetime); (5) abuse of alcohol (more than 14 units a week). Compliance with the inclusion and exclusion criteria was evaluated by means of self-report. Moreover, participants were required to abstain from chocolate, caffeine, and alcohol 12 hours before the experiment and not to use nicotine 2 hours before the session. Cannabis use was also not allowed within 2 days before the study. Subjects' compliance with these criteria was evaluated by means of a personal interview and the application of a saliva drug test, which identified the recent use of cannabis, morphine or cocaine (Oral-View™ Saliva Multi-Drug of Abuse Test; Alfa Scientific Designs Inc., Poway, CA, U.S.A.).

From the initial sample of 61 subjects, one male participant withdrew from the experiment before completing the flanker task, without providing any explanation. Another subject experienced anxiety before cannabis administration and had to quit the study. Regarding adverse events related to drug administration, one participant reported anxiety combined with fatigue and nausea, which led to his exclusion from the experiment. In addition, one female subject requested a break in the experiment, which prevented her from completing the flanker task. Moreover, the data of another participant was excluded from the analysis due to a technical malfunction. In addition, initial screening of the behavioral data revealed that there was one participant with an extremely low percentage (marked as extreme outlier in SPSS, <1st quartile minus 3.0 IQR) of correct trials. Consequently, this subject was excluded from the analyses. This left 55 subjects for the final analysis (49 males and six females).

Study drugs

The active drug substance was composed of the dried, milled and homogenized flowers of the plant *Cannabis sativa* (variety 'Bedrocan'®; 19% THC). It was acquired from Bedrocan BV (Veendam, The Netherlands) where it was cultivated under standardized conditions in line with the requirements of Good Agricultural Practice (GAP). The placebo (variety 'Bedrocan'®; <0.5% THC) administered in the experiment had a moisture content and terpenoid profile (providing the typical smell and taste of cannabis) matching the active drug. Study medication was prepared by ACE Pharmaceuticals BV (Zeewolde, The Netherlands). For each specific dose, precise amounts of active cannabis and placebo were mixed so that each dose was equal to 250 mg total weight but with varying concentrations of THC (placebo/5.5 mg/22 mg THC). Study medication was kept in a refrigerator (2–8°C) in triple-layer laminated foil pouches (Lamigrip). Shelf life stability was determined to be at least 1 year under these conditions.

On the experiment day, each participant was administered a randomized single dose of cannabis by means of a Volcano® vaporizer (Storz&Bickel GmbH, Tüttlingen, Germany)—a safe and reliable method of intrapulmonary administration of THC (Hazekamp et al., 2006; Zuurman et al., 2008). Cannabis was vaporized at a temperature of 230°C into a standard Volcano balloon as supplied with the vaporizer. For the purpose of blinding, the Volcano balloon was covered with a non-transparent plastic bag so that no differences in the density of the vapor were visible between dosages.

When delivering THC by means of vaporizing, it should be noted that the dose present in the plant material is only partially vaporized into the balloon (Hazekamp et al., 2006), and that a part of the THC inhaled from the balloon is not absorbed by the lungs but is exhaled again (Zuurman et al., 2008). Therefore, in order to obtain an absorbed dose of approximately 2 and 8 mg of THC, we loaded the Volcano vaporizer with 5.5 and 22 mg of THC, respectively. Furthermore, since the Volcano vaporizer and cannabis joints deliver comparable amounts of THC (Abrams et al., 2007), the loaded vs. absorbed dose distinction can be applied to smoked cannabis as well.

During administration, subjects were requested to inhale deeply and hold their breath for 10 seconds after each inhalation. They were asked not to speak during the inhalation period and were instructed to empty the balloon within 5 minutes. Subjects had the possibility to practice the inhalation procedure using an empty balloon before drug administration.

Shortened Raven's Standard Progressive Matrices (SPM; measure of intelligence)

Individual IQ test scores were evaluated by means of a reasoning-based intelligence test (Raven et al., 1988). Each element of this test is composed of a pattern or sequence of a diagrammatic puzzle with one item missing. The task is to complete the pattern or sequence by selecting the correct missing piece from a list of choices. The items become more difficult as the test taker proceeds through the test. The SPM test measures an individual's skill for creating perceptual relations and reasoning by analogy independent of language and formal schooling. The version of the test used in the experiment was composed of 14 items.

Flanker task (error monitoring)

In order to measure the ERN and Pe, an adapted version of the Flanker task was used (following Spronk et al., 2011). Subjects were instructed to respond with their right or left index finger to the letter they saw in the center of the screen (H or S), in a congruent (HHHHH or SSSSS) or incongruent (SSHSS or HHSHH) letter string. The assignment of H or S to the left or right index finger press was counterbalanced across subjects. A fixation point was initially presented (lasting 100 ms) with the stimulus following 300 ms later (lasting 100 ms). Afterwards the screen remained blank for 900 ms, followed by a visual feedback screen (lasting 1000 ms). The inter-trial interval was 100 ms. The visual feedback was composed of a yellow, blue, or red rectangle signaling that the previous response was correct, incorrect, or too late, respectively. Subjects were required to make a response as quick as possible to prevent feedback specifying that their reaction was too slow based on an individually determined preset reaction time (RT) deadline. Initially, the subjects were familiarized with the task in a practice block composed of 60 trials, during which the preliminary RT deadline was set at 800 ms. Afterwards, the average RT and SD of the correct responses were computed and the RT deadline was determined for each individual participant by adding 0.5 SD to the mean RT from the practice block. Consequently, this deadline was used during the main task. Note that the inclusion of this RT deadline is crucial to guarantee that error rates do not differ across the experimental conditions (see e.g. de Bruijn et al., 2004, 2006). The main task consisted of five blocks of 100 trials. After each part, subjects received information regarding the amount of incorrect and too late responses. Verbal instructions were provided to maintain response accuracy at around 80–90%.

Visual analogue scales (VAS; subjective measure of drug effects)

Three scales were used to measure the subjective effects of cannabis (horizontal 100-mm lines, the left pole labeled "not at all" and the right "extremely") which refer to "(feeling) High", "Good drug effect (pleasant)", and "Bad drug effect (unpleasant)". Participants were instructed to mark a point at the continuous scale in order to indicate their experience.

EEG recording

EEG activity was recorded over 10 positions: F1, Fz, F2, FC1, FCz, FC2, C1, Cz, C2, and Pz of the 10/10 standard. Bipolar derivations of electro-oculogram (EOG) signals over the left and right outer canthus were used to calculate horizontal eye movements. Vertical eye movements were calculated by bipolar derivations of signals above and below the left eye. Monopolar recordings were referenced to the common mode sensor (CMS) and a driven right leg (DRL) electrode was used for drift correction (for details see http://www.biosemi.com/faq/cms&drl.htm). In order to re-reference the data offline, two electrodes were placed at the left and right mastoid. Signals were DC amplified and digitized with a BioSemi ActiveTwo system (BioSemi B.V., Amsterdam, The Netherlands) with a sampling rate of 512 Hz.

Design and procedure

The study used a randomized, double-blind, placebo-controlled, between-groups (placebo vs. 5.5 mg vs. 22 mg THC) design. All subjects were tested individually. After arrival, the participants were instructed to complete the SPM test within the time limit of 10 minutes. This was followed by the study drug administration. Six minutes after cannabis administration, subjects were instructed to report the subjective effects of the drug using the VAS. The evaluation of drug effects was then repeated twice–at 35 and 60 minutes after administration. After the initial VAS measurement, the subjects completed the Flanker task (in the time frame between 6 and 35 minutes after drug administration) on a computer using a Serial Response Box™ (Psychology Software Tools Inc., Sharpsburg, PA, U.S.A.).

Statistical analysis

Off-line analyses were conducted with Brain Vision Analyzer (Brain Products GmbH, Munich, Germany). After re-referencing the channels to the average mastoid, data was high-pass filtered at 0.01 Hz (24 dB/oct), and ocular artifacts correction was performed using the standard Gratton et al. (1983)

method. EEG artifacts were automatically identified with the use of four criteria: (1) bad gradient (>50 μV/sample), (2) bad max–min difference (>200 μV/200 ms), (3) bad amplitude (absolute value >1000 μV), and (4) low activity (<0.50 μV/100 ms). For the ERN and Pe components, epochs referring to correct and incorrect responses at incongruent trials were averaged individually and time-locked to response onset, starting 100 ms before and finishing 500 ms after the response, relative to a 100-ms pre-response baseline. In order to investigate if the impact of cannabis on the response-locked ERP components was not influenced by a general impairment of information processing or attention, additional stimulus-locked ERPs were analyzed (N1, N2, and P300). For these components, epochs associated with correct responses were averaged separately for congruent and incongruent stimuli time-locked to stimulus onset, starting 100 ms before and finishing 500 ms after the stimulus, relative to a 100-ms pre-stimulus baseline. All ERPs were measured as the baseline-corrected average amplitude across a predetermined interval, relative to the response or stimulus onset. The ERN amplitude was determined on correct and incorrect incongruent trials in the 50- to 100-ms time-window relative to response onset, at electrodes Fz, FCz, and Cz. The Pe was calculated on correct and incorrect incongruent trials in the period between 300 and 400 ms post-response, at electrode Pz. The N1 amplitude was measured in the 65- to 115-ms time-window after stimulus onset, at electrodes FCz, Cz, and Pz. The N2 was determined in the period between 280 and 330 ms post-stimulus, at electrode FCz. The P300 amplitude was measured in the time-window between 350 and 400 ms relative to stimulus onset, at electrodes FCz, Cz, and Pz.

The response-locked ERN was analyzed with the use of a repeated-measures ANOVA, with correctness (correct vs. incorrect) and electrode site (Fz vs. FCz vs. Cz) as within-subjects factors, and condition (placebo vs. 5.5 mg vs. 22 mg THC) as a between-groups factor. A repeated-measures ANOVA was also used to analyze the Pe, with correctness (correct vs. incorrect) as a within-subjects factor, and condition (placebo vs. 5.5 mg vs. 22 mg THC) as a between-groups factor. In the case of the stimulus-locked ERPs, the data was analyzed with the use of a repeated-measures ANOVA, with congruency (congruent vs. incongruent) and electrode site (for N1 and P300 only; FCz vs. Cz vs. Pz) as within-subjects factors, and condition (placebo vs. 5.5 mg vs. 22 mg THC) as a between-groups factor. Moreover, repeated-measures ANOVAs were used to analyze individual means for RTs, with congruency (congruent vs. incongruent) and correctness (correct vs. incorrect) as within-subjects factors, and condition (placebo vs. 5.5 mg vs. 22 mg THC) as a between-groups factor. In the case of

average error rates and percentage of "too late" responses, separate repeated-measures ANOVAs were run for both measures, with congruency (congruent vs. incongruent) as a within-subjects factor, and condition (placebo vs. 5.5 mg vs. 22 mg THC) as a between-groups factor. In addition, in order to investigate post-error slowing (Rabbitt, 1966), we used the optimized measure recommended by Dutilh et al. (2012) that compares RTs of correct responses preceding an error to RTs of correct responses following an error. Only incongruent trials were included in this analysis in order to circumvent serial congruency effects. Consequently, a repeated-measures ANOVA was applied with trial type (pre-error vs. post-error) as a within-subjects factor, and condition (placebo vs. 5.5 mg vs. 22 mg THC) as a between-groups factor.

For the IQ test scores, age, and substance use data, between-groups ANOVAs were conducted with condition (placebo vs. 5.5 mg vs. 22 mg THC) as a between-groups factor. Data referring to sex was analyzed with the use of a Pearson's chi-squared test. VAS scores were analyzed by means of repeated-measures ANOVAs with time after cannabis administration (6 vs. 35 vs. 60 minutes) as a within-subjects factor, and condition as a between-groups factor. All measures were analyzed separately. *Post-hoc* multiple comparisons t-tests were applied with Bonferroni correction. A significance level of $p < 0.05$ was adopted for all tests.

Results

Demographic and substance use data

No significant main effects of condition were found for age ($F(2, 52) = 1.478$, $p = 0.238$), IQ test score ($F(2, 52) = 0.5$, $p = 0.61$), monthly cannabis use ($F(2, 52) = 0.435$, $p = 0.649$), years of cannabis exposure ($F(2, 52) = 1.687$, $p = 0.195$), monthly alcohol use ($F(2, 52) = 0.44$, $p = 0.647$), monthly nicotine use ($F(2, 52) = 1.034$, $p = 0.363$), and years of nicotine exposure ($F(2, 52) = 0.57$, $p = 0.569$). The drug conditions also did not significantly differ by sex ($\chi^2(2, N = 55) = 3.524$, $p = 0.172$). However, there was a significant main effect of condition on years of alcohol exposure ($F(2, 52) = 3.918$, $p = 0.026$); see Table 1.

Table 1 *Demographic and substance use data for each experimental condition.*

	Placebo	5.5 mg THC	22 mg THC	Significance level
N (Male : Female)	19 (18 : 1)	18 (17 : 1)	18 (14 : 4)	n.s.
Age	21.3 (2.3)	21.1 (2.1)	22.3 (2.3)	n.s.
IQ test score	8 (2.5)	7.3 (2.7)	7.1 (2.5)	n.s.
Monthly cannabis use	42.1 (30.6)	51.3 (52.6)	40 (29)	n.s.
Years of cannabis exposure	5.8 (3.1)	4.8 (1.9)	6.3 (2.2)	n.s.
Monthly alcohol use	26.5 (18.1)	23.7 (19.8)	21 (15.4)	n.s.
Years of alcohol exposure	5.5 (2.6)	4.8 (2.5)	7.2 (2.5)	$p = 0.026$
Monthly nicotine use	207.3 (204.2)	121.3 (140)	160.8 (194.3)	n.s.
Years of nicotine exposure	4.5 (3.7)	3.5 (4.2)	4.8 (4.1)	n.s.

Standard deviations in parentheses; n.s.: non-significant difference; Age: reported in years; IQ test score: measured by a shortened version of Raven's Standard Progressive Matrices; Monthly cannabis use: consumption of cannabis cigarettes (joints); Monthly alcohol use: consumption of alcohol units; Monthly nicotine use: consumption of cigarettes.

Behavioral effects

Performance

The percentage of responses for each of the four response options for each trial type and each experimental group is presented in Table 2. The analysis revealed that error rate was higher in incongruent than in congruent trials ($F(1, 52) = 234.172$, $p < 0.001$). Likewise, there were more response omissions in incongruent than in congruent trials ($F(1, 52) = 153.73$, $p < 0.001$). Moreover, there was a significant main effect of condition on response omissions. *Post-hoc* multiple comparisons revealed that subjects in the 22 mg THC condition displayed more omissions than subjects in the placebo condition ($t(35) = 3.828$, $p < 0.001$) and the 5.5 mg THC condition ($t(34) = 3.447$, $p = 0.001$). There were no significant interaction effects ($p > 0.05$).

Table 2 *Mean percentages of correct, incorrect, omission, and too early responses to congruent and incongruent trials for each experimental condition.*

	Congruent			Incongruent		
	Placebo	5.5 mg THC	22 mg THC	Placebo	5.5 mg THC	22 mg THC
% Correct	81.5	73.8	67	55.1	49.4	46.5
% Incorrect	9.4	13.2	11.5	24.4	28.9	22.2
% Omission	8	10.3	19.4	19	18.9	29.1
% Too early	1.1	2.7	2.1	1.5	2.8	2.2

Reaction times

Trials with response omissions were excluded from the analysis (see Figure 1). The ANOVA revealed main effects of congruency ($F(1, 52) = 66.188$, $p < 0.001$) and correctness ($F(1, 52) = 157.788$, $p < 0.001$). Specifically, participants responded faster in congruent trials (299 ms) than in incongruent trial types (315 ms). Moreover, subjects performed faster in incorrect (288 ms) than correct trials (326 ms). There were no significant main effects of condition, or interaction effects ($p > 0.05$).

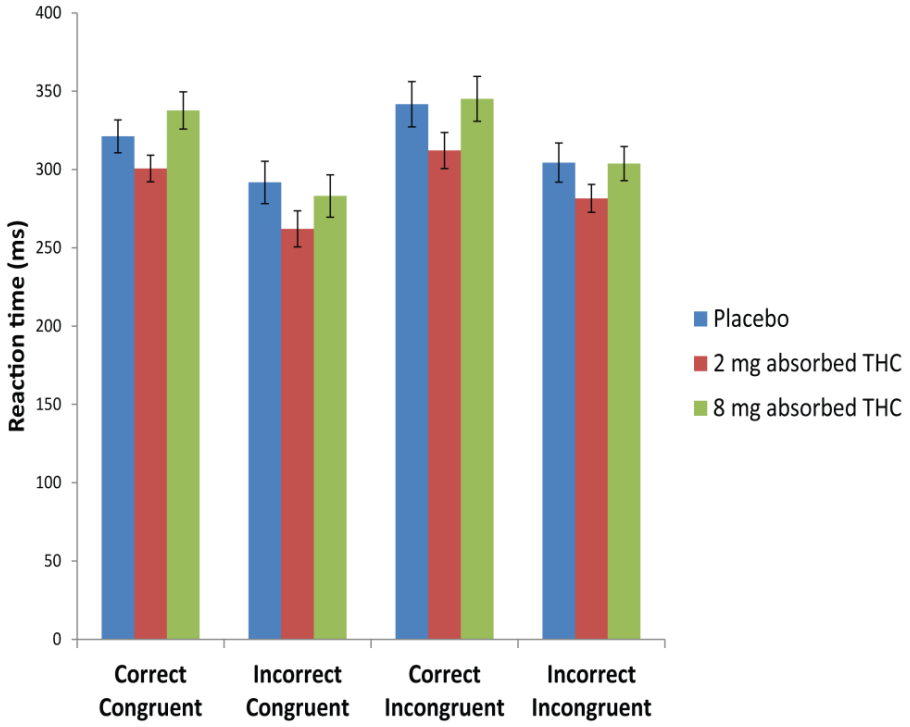

Figure 1 *Average reaction times for correct and incorrect responses in both congruent and incongruent trials for each experimental condition. Error bars represent SE of the mean.*

Post-error slowing

A significant main effect of trial type ($F(1, 52) = 24.408$, $p < 0.001$) indicated that RTs following an incorrect response were significantly higher (328 ms) than those preceding an error (315 ms). There were no significant main effects of condition, or interaction effects ($p > 0.05$).

Drug subjective effects

A significant main effect of time after cannabis administration was found only in the case of the rating of "high" (with Huynh–Feldt correction; $F(1.887, 94.358) = 18.063$, $p < 0.001$). Nevertheless, significant main effects of condition were revealed on all three measures: "high" ($F(2, 50) = 12.477$, $p < 0.001$), "good drug effect" ($F(2, 50) = 11.097$, $p < 0.001$), and "bad drug effect" ($F(2, 50) = 4.918$, $p = 0.011$). There were no significant interaction effects ($p > 0.05$).

Post-hoc multiple comparisons revealed that participants in the placebo condition showed significantly lower ratings of "high" than the 5.5 mg ($t(35) = 3.393$, $p = 0.001$) and 22 mg THC groups did ($t(35) = 4.732$, $p < 0.001$); see Figure 2. Furthermore, the scores of "good drug effect" in the placebo group were significantly lower than those in the 5.5 mg ($t(35) = 3.988$, $p < 0.001$) and 22 mg THC conditions ($t(35) = 2.991$, $p = 0.009$); see Figure 3. For the measures of "high" and "good drug effect", no significant differences were obtained between the ratings in the 5.5 mg and 22 mg THC conditions ($p > 0.05$). In contrast, in the case of the ratings of "bad drug effect", subjects in the 22 mg THC group displayed significantly elevated scores, compared to those in the placebo ($t(35) = 2.882$, $p = 0.025$) and 5.5 mg THC groups ($t(34) = 2.923$, $p = 0.025$); see Figure 4. Moreover, the scores of "bad drug effect" did not significantly differ between the placebo and 5.5 mg THC groups ($p > 0.05$).

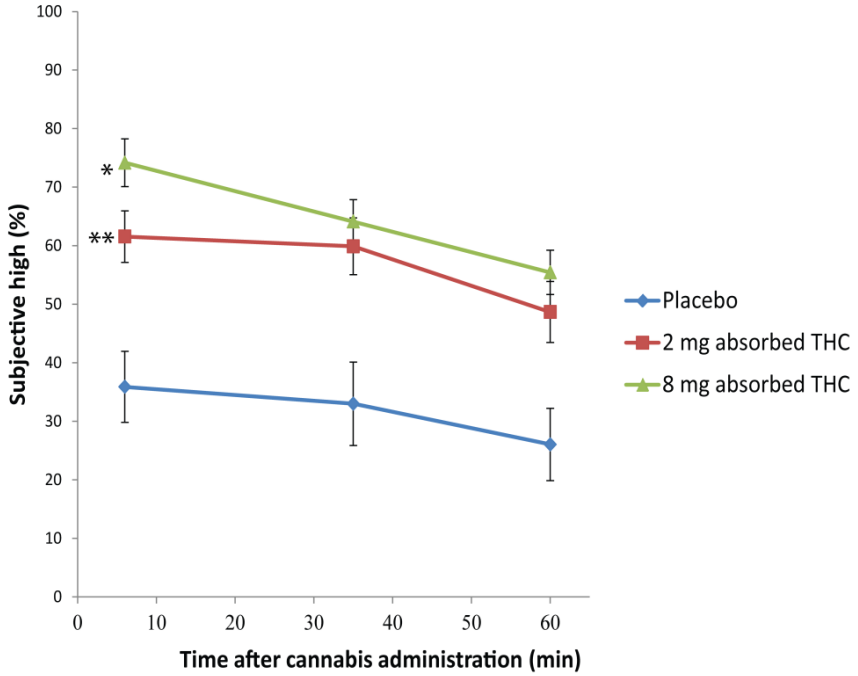

Figure 2 *Average subjective high (rated as a percentage) experienced in each experimental condition as a function of time after cannabis administration. Symbols indicate a significant ($p < 0.01$) difference between the 22 mg THC and placebo groups (*), and between the 5.5 mg THC and placebo groups (**). Error bars represent SE of the mean.*

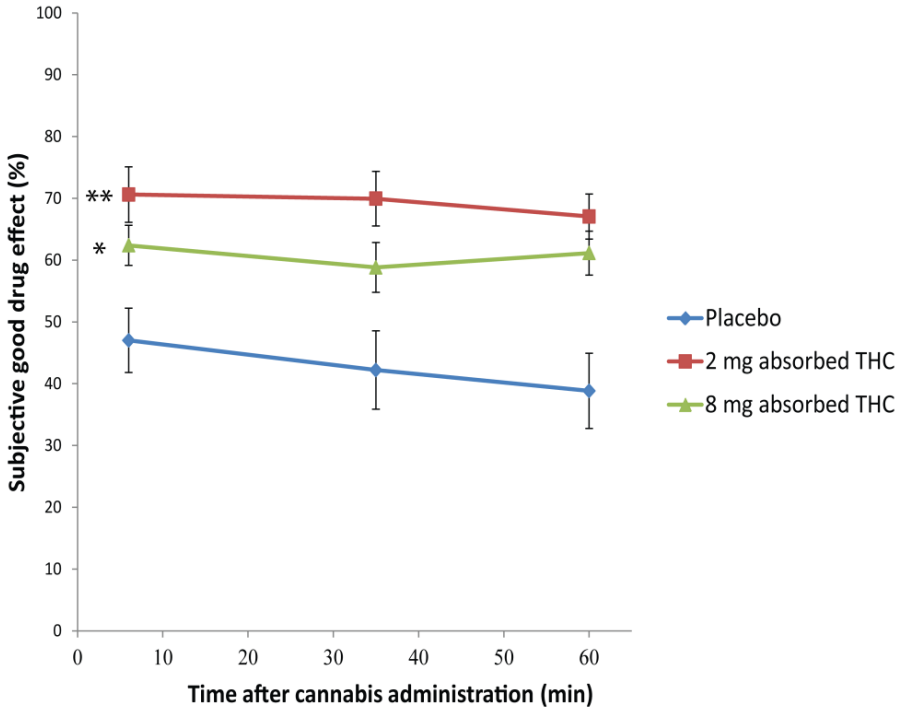

Figure 3 *Average subjective good drug effect (rated as a percentage) experienced in each experimental condition as a function of time after cannabis administration. Symbols indicate a significant ($p < 0.01$) difference between the 22 mg THC and placebo groups (*), and between the 5.5 mg THC and placebo groups (**). Error bars represent SE of the mean.*

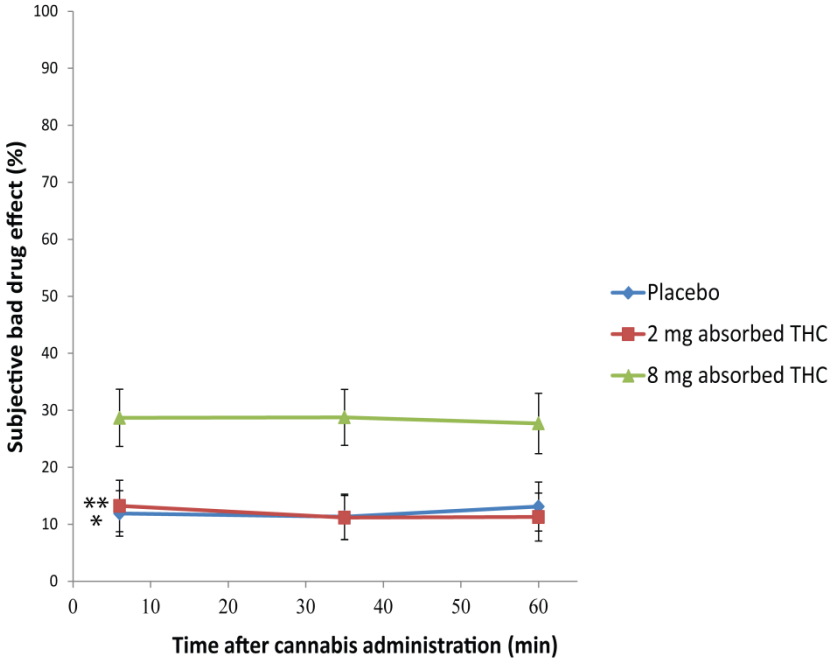

Figure 4 *Average subjective bad drug effect (rated as a percentage) experienced in each experimental condition as a function of time after cannabis administration. Symbols indicate a significant ($p < 0.05$) difference between the placebo and 22 mg THC groups (*), and between the 5.5 mg and 22 mg THC groups (**). Error bars represent SE of the mean.*

ERP analyses

ERN amplitude

The response-locked ERP components for the three drug conditions are displayed in Figure 5. A significant interaction was found between condition and correctness ($F(2, 52) = 4.351$, $p = 0.018$), but not between condition, electrode, and correctness ($p > 0.05$). There was also a significant interaction between electrode and correctness ($F(2, 104) = 11.895$, $p < 0.001$). In addition, significant main effects of electrode ($F(2, 104) = 13.299$, $p < 0.001$), correctness ($F(1, 52) = 110.018$, $p < 0.001$), and condition ($F(2, 52) = 3.644$, $p = 0.033$) were found. A separate between-groups ANOVA revealed that the main effect of condition was driven only by incorrect responses in the case of all three electrodes: Fz ($F(2, 52) = 4.13$, $p = 0.022$), FCz ($F(2, 52) = 4.99$, $p = 0.01$), and Cz ($F(2, 52) = 5.768$, $p = 0.005$).

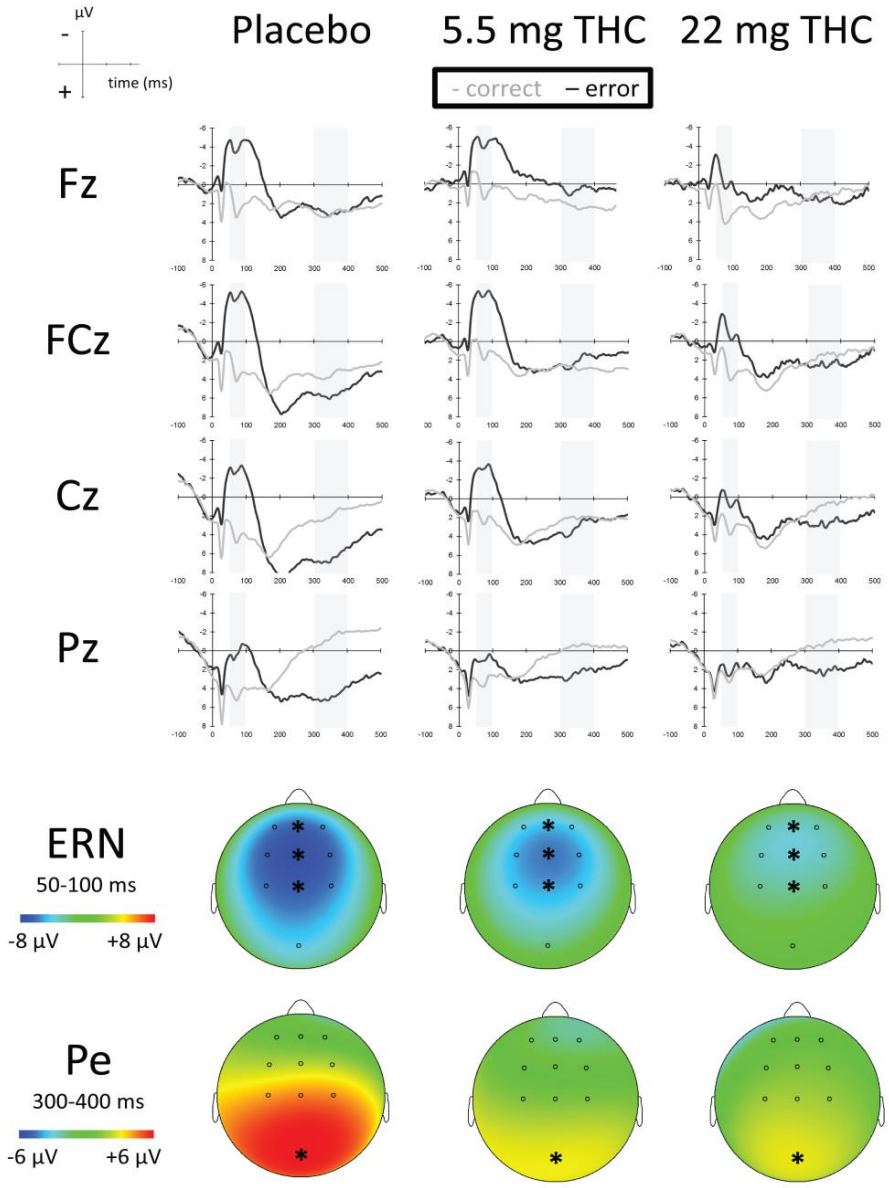

Figure 5 *Grand average response-locked waveforms and topographical distributions of the difference between incorrect and correct responses at incongruent trials for each experimental condition.*

Post-hoc multiple comparisons of the ERN collapsed across the three electrodes (Fz, FCz, and Cz) showed that participants in the 22 mg THC condition displayed a significant decrease in amplitude of the ERN between correct and incorrect responses, as compared to placebo ($t(35) = 2.915$, $p = 0.014$; −3.4 vs. −7.1 μV), but not 5.5 mg THC ($t(34) = 1.738$, $p = 0.333$; −3.4 vs. −5.5 μV). In addition, there was no significant difference between the 5.5 mg THC and placebo conditions ($t(35) = 1.239$, $p = 0.595$; −5.5 vs. −7.1 μV).

Pe amplitude

For the response-locked Pe amplitude, a significant interaction between condition and correctness was found ($F(2, 52) = 5.184$, $p = 0.009$). In addition, there was a main effect of correctness ($F(1, 52) = 65.855$, $p < 0.001$).

Post-hoc multiple comparisons showed that participants in the 22 mg THC condition demonstrated a significant decrease in the amplitude of the Pe between correct and incorrect responses, as compared to placebo ($t(35) = 2.909$, $p = 0.022$; 2.8 vs. 6.2 μV), but not 5.5 mg THC ($t(34) = 0.04$, $p = 1.0$; 2.8 vs. 2.9 μV). Moreover, subjects in the 5.5 mg THC condition significantly differed from those in the placebo condition with regard to this measure ($t(35) = 2.615$, $p = 0.024$; 2.9 vs. 6.2 μV).

N1 amplitude

The stimulus-locked ERP components for the three drug conditions are presented in Figure 6. For the stimulus-locked N1 amplitude a main effect of electrode was found ($F(2, 104) = 35.765$, $p < 0.001$). There were no significant main effects of condition, or interaction effects ($p > 0.05$).

N2 amplitude

In the case of the stimulus-locked N2 amplitude, a main effect of congruency was revealed ($F(1, 52) = 53.629$, $p < 0.001$). There were no significant main effects of condition, or interaction effects ($p > 0.05$).

P300 amplitude

For the stimulus-locked P300 amplitude main effects of electrode ($F(2, 104) = 20.329$, $p < 0.001$) and congruency were found ($F(1, 52) = 32.769$, $p < 0.001$). There were no significant main effects of condition, or interaction effects ($p > 0.05$).

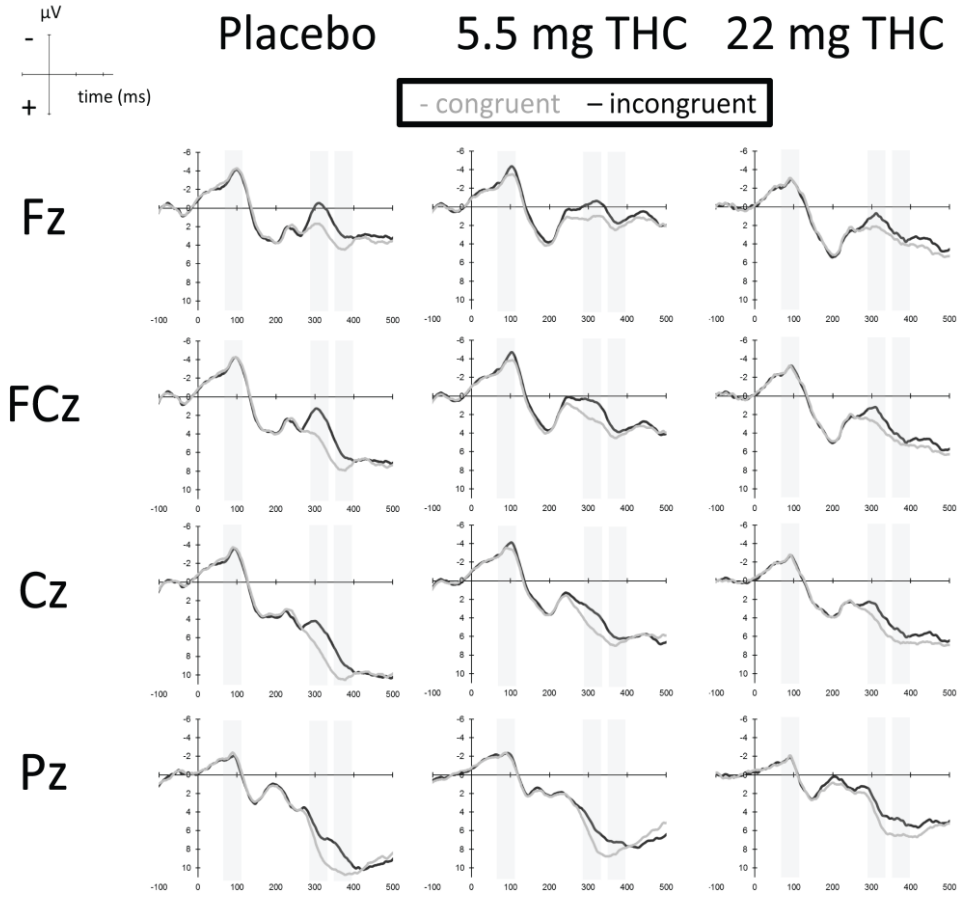

Figure 6 *Grand average stimulus-locked waveforms of the difference between congruent and incongruent trials at correct responses for each experimental condition.*

Discussion

The present study shows for the first time that a low (5.5 mg THC) and high (22 mg THC) dose of vaporized cannabis differentially affects the neural correlates of error monitoring in frequent cannabis users. Specifically, a diminished ERN was observed in the high dose group in comparison to the placebo condition, whereas a diminished Pe amplitude was observed in both the high and low dose conditions, as compared to placebo.

Based on the available research, the finding of a decreased ERN in the high dose condition allows the speculation that a high dose of cannabis might affect the transmission of a reinforcement learning signal to the ACC (Holroyd and Coles, 2002; but see Yeung et al., 2004). Furthermore, the observation of a reduced Pe in both the high and low dose groups may suggest that even a relatively low dose of cannabis is already sufficient to influence the late (elaborate) neural processing of errors as reflected in the Pe. Previous research has linked the Pe to conscious detection of errors (Nieuwenhuis et al., 2001; Endrass et al., 2005), and the temporal dynamics of the Pe have been directly correlated with the emergence of error awareness (Murphy et al., 2012). Based on this, it might be speculated that a low dose of cannabis is sufficient to affect error awareness, although such an assumption needs confirmation in future studies using independent behavioral measures.

Moreover, whereas previous studies on the chronic effects of cannabis use have shown that users are typically tolerant to most of the detrimental effects of cannabis (Hart et al., 2001; Kelleher et al., 2004; D'Souza et al., 2008; Ramaekers et al., 2009; Hart et al., 2010; Theunissen et al., 2012), and recruit compensatory mechanisms to prevent performance being affected (Harding et al., 2012; Fridberg et al., 2013), we showed that acute administration of cannabis still impacts the neural correlates of processes involved in error monitoring. Accordingly, based on the current observations and on the assumption that the ERN and Pe reflect two dissociable processes involved in error monitoring (Nieuwenhuis et al., 2001), it may be assumed that the changes in the neural correlates of the error monitoring system observed in the current study are dose-dependent. Specifically, a high dose of cannabis seems to influence both the conscious (late) and the initial automatic processes involved in error monitoring, whereas a low dose of cannabis appears to affect only the conscious (late) processing of errors.

These potential dose-dependent effects of cannabis on the error monitoring system suggested by our data are in line with an earlier study pointing to dose-dependent effects of cannabis on executive control functions (Ramaekers et al., 2006). In particular, cannabis has been shown to diminish performance on a task measuring executive control (Tower of London), with a high dose of cannabis (500 µg/kg body weight THC) leading to a more pronounced deterioration of performance than a low dose (250 µg/kg body weight THC; Ramaekers et al., 2006). Consequently, combining this with various dose-dependent effects of cannabis on neural correlates of cognitive functions and subjective effects (Hart et al., 2001; Hart et al., 2010; D'Souza et

al., 2012; Hunault et al., 2014), one may speculate that the differential impact of the doses used in the current study reflects a dose-response relationship between cannabis and more general processes underlying executive function, including error monitoring.

Limitations

A significant limitation of the current study is its between-groups design, which at least theoretically raises the possibility that the observed differential impact of the cannabis doses was due to specific features of the studied sample. Another limitation was the lack of measurement of THC blood plasma levels, which did not allow us to assess the correlation between THC in the bloodstream and emergence of drug effects. In addition, the lack of this measurement makes it difficult to evaluate a dose–response curve, as it is possible that there were significant between-subjects differences in absorbed THC due to the lack of standardization of the duration and number of inhalations from the Volcano balloon. Furthermore, the application of a saliva test in order to verify the compliance of participants with the no-consumption criteria was not optimal, since it only provided an approximation of recent use of drugs. Evaluation of urinary levels of THC metabolites (11-COOH-THC) would have been a more accurate measure of drug use over an extended period of time. In addition, including a test for alcohol intoxication would have been another improvement in securing the compliance of subjects with the study requirements. Moreover, it is possible that the observed results were affected by the fact that some subjects could had been experiencing cannabis withdrawal symptoms on the day of testing, due to the requirement to be abstinent from cannabis for 2 days prior the study (Bonnet et al., 2014).

Conclusion

The results of this ERP study show that even a low dose of cannabis may have an effect on the neural correlates of error monitoring of frequent cannabis users. Furthermore, this impact is more pronounced with highly-potent cannabis. Although any such speculations need to be confirmed by future studies, these observations raise the possibility that intoxicated frequent cannabis users might have difficulties to adapt to changing circumstances by monitoring and correcting their erroneous behavior. Consequently, it might be worthwhile to investigate the effects of using cannabis in situations which require flexible updating of behavior to changing conditions. Since such situations require efficient continuous error monitoring processes, any

potential disturbances evoked by cannabis may lead to counterproductive, if not risky, results.

5

The impact of cannabidiol on cognitive and emotional processing*

* This chapter is based on:

Kowal MA, Hazekamp A, Colzato LS, van Steenbergen H, Hommel B (2013) Modulation of cognitive and emotional processing by cannabidiol: the role of the anterior cingulate cortex. Frontiers in Human Neuroscience 7. DOI: 10.3389/fnhum.2013.00147

Introduction

Cannabis sativa is a plant containing over 70 active compounds called cannabinoids (Schoedel and Harrison, 2012). The psychoactive effects of cannabinoids are abused worldwide by about 20% of young people, who report regular or heavy use of the cannabis plant (Moore et al., 2007). Delta-9-tetrahydrocannabinol (THC), the most prevalent cannabinoid in the plant, has been found to be responsible for producing most of the desirable effects of marijuana (Gaoni and Mechoulam, 1964). In line with that, the use of modern hydroponic cannabis farms has resulted in growing strains containing higher levels of THC, while keeping other cannabinoids at negligible levels (Hardwick and King, 2008). Accordingly, it may be assumed that the presence of THC-dominated cannabis plants on the market leads to the risk of more severe consequences of abuse, since THC has been associated with induction of psychotic symptoms both in an acute intoxicated state (D'Souza et al., 2004) and in the long-term (Kuepper et al., 2010). Consequently, in the current paper we propose that cannabidiol (CBD), another abundant compound of cannabis, might have an impact on cognition and emotional processing, which is opposite to the effect of THC. Moreover, we suggest that the effects of CBD would be worth investigating in regard to the modulatory role of the anterior cingulate cortex (ACC)—a brain region where both affective and cognitive information converge (Bush et al., 2000; Botvinick et al., 2001; Paus, 2001).

The pharmacology of CBD is well studied (for a review see: Mechoulam et al., 2002). Its effects are distinct and frequently opposite to those of THC (Fusar-Poli et al., 2012). Whereas THC is a cannabinoid receptor type 1 and 2 (CB1r and CB2r) agonist, CBD has low affinity and a partially antagonistic effect at these receptors (Pertwee, 2008). Furthermore, CBD has been shown to be a serotonin receptor (5-HTr) agonist (Campos and Guimarães, 2008; Zanelati et al., 2010; Gomes et al., 2011). In recent years CBD has received renewed attention from researchers, mainly due to its anxiolytic (e.g. Zuardi et al., 1982; Zuardi et al., 1993; Crippa et al., 2004; Fusar-Poli et al., 2009; Crippa et al., 2011; Bergamaschi et al., 2011) and antipsychotic effects (e.g. Zuardi et al., 2009; Bhattacharyya et al., 2010; Schubart et al., 2011). The therapeutic value of CBD in clinical contexts is currently being explored (Zuardi et al., 2006; Zuardi et al., 2009; Hallak et al., 2010). Moreover, in a recent review Schier et al. (2012) suggested that CBD neither produces psychoactive effects, nor has an impact on cognition. In the light of up-to-date research, this claim may be considered unwarranted, since CBD has been shown to differ with THC in

terms of activation of brain regions during tasks involving response inhibition (Borgwardt et al., 2008), emotional processing (Fusar-Poli et al., 2009), and verbal memory (Bhattacharyya et al., 2010). Additionally, as far as only the anxiolytic effect of CBD is considered, it may be assumed that it influences cognition through, for instance, reducing attention bias toward threatening stimuli (Bar-Haim et al., 2007). In spite of that, the effect of CBD on cognitive performance has been largely unexplored.

Effect of CBD on the ACC

CBD is associated with increased resting cerebral regional blood flow (rCBF) in the left parahippocampal gyrus and decreased rCBF in the amygdala-hippocampus complex, including the posterior cingulate cortex (Crippa et al., 2004). A functional neuroimaging (fMRI) study found evidence for attenuation of the blood-oxygen level dependent (BOLD) signal in the amygdala and the posterior and anterior cingulate cortex in response to the presentation of fearful faces, combined with a reduction in subjective anxiety (Fusar-Poli et al., 2009). CBD also disrupts the functional connectivity between the ACC and amygdala (Fusar-Poli et al., 2010). Taken together, these results point to both an anxiolytic effect of CBD and a critical modulatory role of the ACC. However, Bhattacharyya et al. (2010) found no effect of CBD on ACC activity in a task identical to the one used by Fusar-Poli et al. (2009)—a discrepancy we will be getting back to. To summarize, apart from the emotion-regulating properties of CBD, the CBD–ACC relationship has not been systematically investigated.

Accordingly, it would be worthwhile to examine how the impact of CBD on ACC activity may extend to the domain of cognitive performance. Since modulation of ACC activity is assumed to be the mechanism through which CBD affects brain connectivity during emotional processing (Fusar-Poli et al., 2010), it might be suspected that the ACC is also the main target for CBD in terms of potential cognition-altering effects of the compound. Previous research has identified the ACC as an important relay station for cognitive control processes and as a region that integrates cognitive and emotional information (Bush et al., 2000; Botvinick et al., 2001; Paus, 2001). It is then possible that CBD has an effect on conflict monitoring—a process which monitors for the presence of conflicts in information processing. Conflict monitoring exerts top-down control over information processing by focusing attention on task-

relevant processing streams, while blocking off task-irrelevant channels (Botvinick et al., 2001). In line with that, positron emission tomography (PET) and fMRI studies reliably show ACC activation in tasks in which subjects need to override automatic, but otherwise task-irrelevant responses, such as the Stroop Color Word Test (SCWT; Pardo et al., 1990; Carter et al., 1995; Bush et al., 1998) and go/no-go tasks (Casey et al., 1997; Kawashima et al., 1996). Since CBD has been shown to decrease activity in the ACC (Fusar-Poli et al., 2009; Fusar-Poli et al., 2010), it may be suspected that individuals treated with CBD are less likely to suppress their dominant response (Casey et al., 1997), or become aware of committing a mistake (Holroyd and Coles, 2002).

Effect of CBD on cognition

Taken together, research regarding the impact of CBD on ACC activity appears to be contradictory (see: Table 1): CBD has been reported to attenuate ACC activity (Fusar-Poli et al., 2009; Fusar-Poli et al., 2010), have no effect (Borgwardt et al., 2008; Bhattacharyya et al., 2009; Bhattacharyya et al., 2010), or even enhance ACC activity (Bhattacharyya et al., 2010). One possible explanation for these contradictory observations may be found in the type of tasks used in the studies mentioned and, thus, the functions which they relate to. In the case of cognition, keeping in mind the involvement of the ACC in conflict monitoring (Bush et al., 2000; Botvinick et al., 2001; Paus, 2001), it would be worthwhile to have a closer look at the findings of Bhattacharyya et al. (2010). The observed increased activity of the ACC during a verbal recall task is in line with research showing a lack of impairment of verbal memory in cannabis users intoxicated with high-CBD content cannabis (4.61% on average), as opposed to those who used low-CBD content plant material (0.08% on average; Morgan et al., 2010). Furthermore, it has been suggested that the memory-protective effect of CBD extends into the long-term (Morgan et al., 2012). Combining the results of the above-mentioned studies, one could claim that the CBD-induced improvement is not restricted to the domain of memory itself, but reflects a more general enhancement of the conflict monitoring system.

Table 1 *Functional MRI studies of the cognitive and emotional effects of cannabidiol.*

Cognition	**Sample size**	**CBD dose*** **	**Route**	**Task**	**ACC activation**	**Amygdala activation**	**Anxiolytic effect**
Borgwardt et al. (2008)	15	600 mg	Oral	Response inhibition (go/no-go)	*n.s.*	*n.s.*	$p = 0.06$
Bhattacharyya et al. (2009)	15	600 mg	Oral	Verbal paired associate learning	*n.s.*	*n.s.*	*n.s.*
Bhattacharyya et al. (2010)*	15	600 mg	Oral	Verbal paired associate learning	$p < 0.01$	*n.s.*	$p = 0.06$
Emotion	**Sample size**	**CBD dose*** **	**Route**	**Task**	**ACC activation**	**Amygdala activation**	**Anxiolytic effect**
Fusar-Poli et al. (2009)	15	600 mg	Oral	Facial Expressions of Emotion: Stimuli and Tests	$p < 0.05$	$p < 0.05$	$p = 0.06$
Bhattacharyya et al. (2010)*	15	600 mg	Oral	Facial Expressions of Emotion: Stimuli and Tests	*n.s.*	$p < 0.05$	$p = 0.06$
Fusar-Poli et al. (2010)**	15	600 mg	Oral	Facial Expressions of Emotion: Stimuli and Tests	$p < 0.05$	$p < 0.05$	n/a

* Contrasted with effects of delta-9-tetrahydrocannabinol (10 mg, 99.6 % pure)
** Dynamic causal modeling – significant activation indicating a difference in the forward intrinsic connection between ACC and amygdala.
*** 99.9 % pure in all studies.

Additionally, such a claim becomes somewhat more plausible when one takes into account a recent investigation which found a trend for decreased response latency to oddball stimuli following CBD administration together with, surprisingly, an attenuating effect on the medial prefrontal cortex (Bhattacharyya et al., 2012). Although this opposite effect of CBD on activation and the finding of no effect of CBD on ACC activity in another study applying the verbal recall task make the case less clear (Bhattacharyya et al., 2009), it is possible that the beneficial effect of CBD is more visible in the case of modulating the deteriorating effects of THC than when administered alone. Since THC is a CB1r and CB2r agonist, the opposite, partially antagonistic, effect of CBD on CB1rs and CB2rs suggests that it may protect against the deterioration of cognitive performance caused by THC (Pertwee, 2008). THC has been shown to decrease the error-related negativity—an event-related potential indicative of conflict monitoring and assumed to be generated by the ACC (Spronk et al., 2011). Given the opposing neuropharmacological actions of the two compounds, one may then expect that CBD will inhibit the impact of THC on the ACC. On the other hand, in the absence of THC, partial antagonism of CB1rs might not be sufficient to produce overt changes in the conflict monitoring system, either at the behavioral or the neurophysiological level. Accordingly, it would be worthwhile to explore whether the THC-protective effects of CBD can be related directly to ACC functioning.

Effect of CBD on affective processing

It is also interesting to consider the ACC-mediated impact of CBD on emotional processing. Animal research indicates that the anxiolytic effect of CBD depends on action of the compound on specific brain areas and that the effect could also, in some cases, be anxiogenic (Marco et al., 2011). In the case of human studies, it can be hypothesized that CBD decreases ACC activity, which would be in line with the anxiolytic effect of the compound (Fusar-Poli et al., 2009). The concurrent reduction in amygdala BOLD response associated with presentation of fearful faces gives further support to this assumption, given the involvement of this region in fear processing and its anatomical connection with the ACC (Fusar-Poli et al., 2009; Bhattacharyya et al., 2010; Fusar-Poli et al., 2010). However, while both Fusar-Poli et al. (2009) and Bhattacharyya et al. (2010) found a trend in reduction of subjective anxiety following CBD administration, only the former was able to observe a related

decrease in ACC activation during emotional processing. In the case of the latter, the authors explain the lack of a possible effect by a selective analysis of brain areas where THC and CBD had opposite effects, instead of assessing the effects of the two compounds separately (Bhattacharyya et al., 2010). However, the fact that application of the same design, task, and subject sample led to different results throws some doubt on the importance of the ACC in mediating the effects of CBD on brain connectivity (Fusar-Poli et al., 2010). Moreover, if one were to follow the logic of Fusar-Poli et al. (2010) about top-down control of the ACC over the amygdala, attenuation of the amygdala BOLD response in the Bhattacharyya et al. (2010) study should not have been observed without a simultaneous effect in the ACC. In principle, the anxiolytic effects of CBD are assumed to be mediated by the ACC, which, in turn, affects activity of the amygdala (Fusar-Poli et al., 2010). Therefore, from this perspective, it is surprising that the reduction in subjective anxiety observed by Bhattacharyya et al. (2010) was indeed associated with a concurrent decrease in amygdala activation, but not the ACC. If the ACC actually plays a critical role in moderating the anxiolytic effects of CBD (Fusar-Poli et al., 2010), then it seems plausible to expect an effect in this brain region, even when keeping in mind the selective analysis of opposing effects of THC and CBD on activation (Bhattacharyya et al., 2010). On the other hand, the absence of an effect of CBD may alternatively be explained by the lack of a significant linear relationship between the effects of the two drugs and placebo. Consequently, the fact that Bhattacharyya et al. (2010) did not find CBD to be associated with decreased ACC activity is not necessarily equivalent to the lack of an effect of CBD relative to a placebo condition. In any case, apart from evidence pointing to a link between CBD and the ACC in emotional processing, it is likely that this connection is not as straightforward as suggested by Fusar-Poli et al. (2010).

Summary

In sum, existing research seems to undermine Schier's et al. (2012) suggestion regarding the lack of a relationship between CBD and cognition. Rather, it seems that both cognitive and affective consequences of CBD administration may be mediated by the ACC. However, the lack of clear-cut results renders the extent and nature of this modulation unclear. The diversity of findings may be explained by various factors, including differential

activation of the cognitive and affective subdivisions of the ACC (Bush et al., 2000), the slow onset of action and inconsistent bioavailability of orally administered cannabinoids (Hazekamp et al., 2006), the dosage of CBD (Marco et al., 2011), or whether CBD was administered alone, or in combination with THC (Pertwee, 2008). Furthermore, since modulation of the cognitive effects of cannabinoids has been linked to polymorphism of the cannabinoid receptor (CNR1) gene (Ho et al., 2011; Stadelman et al., 2011), it is possible that some genetic predispositions of the studied samples could have influenced the results. From this perspective, also the catechol-O-methyltransferase (COMT) gene seems to be a plausible moderating factor due to its role in cognitive control (Colzato et al., 2010) and the pharmacological interactions between the endocannabinoid and dopamine systems (Fattore et al., 2010). In any case, inclusion of new variables could further clarify the CBD–ACC relationship and its role in the aspects of conflict monitoring and emotional processing.

6

Summary and general discussion

Summary and general discussion

In this thesis we investigated the acute, as well as chronic, effects of cannabis on the mechanisms underlying cognitive functions in a population of regular cannabis users. We carried out experiments in order to study the impact of cannabis on dopaminergic functioning, creative processes, and error monitoring. Moreover, we also reviewed the available scientific evidence regarding the effects of cannabidiol (CBD) on emotional and cognitive processing.

First, the experiment presented in chapter 2 suggests that long-term cannabis use detrimentally affects dopaminergic functioning in the human stratum. The measurement of spontaneous eye-blink rate (EBR; a clinical marker of striatal dopamine [DA] transmission; Karson, 1983; Shukla, 1985; Taylor et al., 1999) among regular cannabis users and non-user controls with comparable demographic characteristics demonstrated a significant difference between the two groups. Specifically, cannabis users showed a decrease in their EBR, as compared to non-users. The results suggest that chronic cannabis use may impair dopaminergic transmission in the striatum indirectly through complex interactions with the endocannabinoid system (Hoffman et al., 2003; Fattore et al., 2010; Fernández-Ruiz et al., 2010).

Second, the results presented in chapter 3 demonstrated impaired divergent thinking performance of regular cannabis users intoxicated with a high dose of delta-9-tetrahydrocannabinol (THC; 22 mg) in the form of vaporized herbal cannabis, as compared to users administered a low dose of THC (5.5 mg) or placebo. Divergent thinking occurs when trying to find as many solutions as possible to a problem without a clear definition (i.e. "brainstorming"). It is considered a mental process which is crucial to creative performance (Guilford, 1967) and linked to the functioning of striatal DA (Akbari Chermahini and Hommel, 2010). In the case of our study, although we considered the impaired creative performance of subjects as a possible consequence of induced distractibility due to supra-optimal levels of DA in the striatum (Cools and D'Esposito, 2011), this suggestion seems to be less likely in the light of new findings on DA and THC (Bossong et al., 2015). Future neuroimaging research is required to better understand the neural mechanisms underlying the effects of cannabinoids on divergent thinking and other related creative processes. It would be worthwhile to more thoroughly explore the link between cannabis and creativity, considering the widespread belief about cannabis as a creativity-enhancer (e.g. Green et al., 2005). Possibly,

introduction of a motivational factor to a study might contribute to a higher ecological validity of its results. Specifically, if a cannabis user considers a creative task personally relevant, then the results of the task may provide a better representation of the creative performance of the subject outside the laboratory setting. This would be in line with anecdotal reports of cannabis users, who claim to use cannabis as a creativity-enhancer typically in situations which they find personally rewarding.

Third, the experiment described in chapter 4 presented data on a dose-dependent impact of vaporized cannabis on the neural correlates of error monitoring in chronic cannabis users. It was demonstrated that two event-related potentials (ERPs) related to the recognition of discrepancies between expected and executed actions—the error-related negativity (ERN) and error positivity (Pe)—were differentially affected by the THC doses administered in the study. Specifically, a high dose of THC (22 mg) led to diminished ERN and Pe amplitudes in comparison to placebo, while a low THC dose (5.5 mg) resulted only in a reduced Pe amplitude, as compared to placebo. Moreover, there is evidence suggesting that the ERN and Pe represent separate processes involved in the monitoring of errors (Nieuwenhuis et al., 2001) and that the Pe is linked to the conscious awareness of errors (Nieuwenhuis et al., 2001, Endrass et al., 2005; Murphy et al., 2012). Consequently, we suggested that a high dose of cannabis influences both the initial automatic processing of errors and the conscious (late) error monitoring stages. Conversely, only the conscious (late) recognition of discrepancies between expected and executed actions appears to be affected by a low cannabis dose. Nevertheless, in order to confirm these assumptions, research including independent behavioral measures would be needed. Possibly, combining the acquisition of ERPs with the introduction of a manual response that indicates the awareness of committing an error by the subject could provide interesting information in this regard.

Fourth, chapter 5 presented a review of available neuroimaging research on the effect of CBD on affective and cognitive processing. We reviewed evidence indicating a critical role of the anterior cingulate cortex (ACC) in this regard. The results were contradictory: CBD has been found to attenuate ACC activity (Fusar-Poli et al., 2009; Fusar-Poli et al., 2010), have no effect (Borgwardt et al., 2008; Bhattacharyya et al., 2009; Bhattacharyya et al., 2010), or even enhance ACC activity (Bhattacharyya et al., 2010). Moreover, although the exact mechanism by which this occurs is unclear, we suggested that the modulation of ACC activity by CBD may lead to enhanced processing of errors due to a critical role of the ACC in this process (Bush et al., 2000;

Botvinick et al., 2001; Paus, 2001; Shackman et al., 2011) and results suggesting an opposing effect of CBD on executive control functions, when compared with THC (Bhattacharyya et al., 2010; Morgan et al., 2010, 2012).

Combining the information presented in chapters 4 and 5, it seems crucial to inquire into the relationship between cannabis and error monitoring in order to better understand the impact of using cannabis on everyday life. Specifically, since the lack of the ability to modify one's behavior in the face of changing circumstances and negative consequences is a core clinical symptom of drug dependence (Kalivas and Volkow, 2005), and deteriorated learning from errors is related to poor addiction treatment outcomes (Luo et al., 2013; Marhe et al., 2013), knowledge of the effects of cannabis on the capacity to detect and correct errors in one's behavior may be of importance in designing an effective addiction treatment program. Research on the long-term effects of using cannabis strongly suggests that the error monitoring capacity of regular users is impaired (Tapert et al., 2007; Hester et al., 2009; Falkenstein et al., 2013; Nicholls et al., 2015; Carey et al., 2015). Consequently, since the study presented in chapter 4 demonstrated that THC-rich cannabis may be detrimental to the processing of errors, it would be worthwhile to examine the supposedly contradictory effect of CBD on this process. Aside from the possibility that CBD may reduce the acute THC-induced impairment, it would be even more interesting to investigate whether the protective effect of CBD extends into the long-term, as suggested by some researchers (Morgan et al., 2012). If that is the case, it might be worthwhile to explore the therapeutic application of CBD in the treatment of cannabis dependence.

Nevertheless, it would be valuable to evaluate the findings presented in this thesis in the light of new evidence. In particular, up-to-date neuroimaging research indicates that regular cannabis use by adults does not lead to significant differences in DA D_2/D_3 receptor availability or DA release in the striatum (Stokes et al., 2012; Urban et al., 2012; Mizrahi et al., 2013; Volkow et al., 2014). On the other hand, Bloomfield et al. found deteriorated striatal DA synthesis capacity in cannabis users (2014a) and suggested this to be correlated with reduced reward sensitivity and reduced motivation associated with chronic cannabis use (2014b). Moreover, it has been suggested that the degree of impairment of dopaminergic transmission is positively correlated with the age of onset of cannabis use (Urban et al., 2012; Bloomfield et al., 2014a). Consequently, neuroimaging studies on the effects of regular cannabis use on dopaminergic functioning are not conclusive. From this perspective,

although we were able to find a robust reduction in the EBR of regular cannabis users, the results of our research require further investigation.

However, a recent study by Bossong et al. (2015) re-analyzed the data of two previous studies on the acute effects of THC on DA transmission in the striatum (Bossong et al., 2009; Stokes et al., 2009). It was found that the increase in DA release after THC administration is modest, compared to that with other recreational drugs of abuse, like amphetamine or nicotine. Since THC administration leads to potent behavioral effects, it was suggested that these overt effects of the drug are unlikely to be exclusively dependent on striatal dopaminergic functioning. Possibly, the behavioral effects of THC may be mediated directly by the endocannabinoid system, although the exact mechanism by which this could occur is unclear (Bossong et al., 2015). In any case, taken together, the research on both the chronic and acute effects of cannabinoids on striatal DA suggests that cannabis may detrimentally affect the proper functioning of this neurotransmitter. On the other hand, a potential dopaminergic impairment is unlikely to be severe in the long-term. Possibly, the age of onset of cannabis use is a crucial aspect in this regard. Consequently, more research is needed to better understand the relationship between dopaminergic functioning of chronic cannabis users and the psychosis-inducing effects of cannabis (Kuepper et al., 2010).

In summary, the mechanisms by which cannabis affects cognition and related neural functioning are complex and not yet fully understood. The pharmacological complexity of the cannabis plant and the widespread distribution of the endocannabinoid system in the human body, which interacts with other neuromodulatory systems in a variety of ways, seem to be the main factors contributing to this state of things. Combined with the legal limitations regarding the investigation of a prohibited drug, this complexity makes it difficult to study the effects of cannabis in any area, including cognition. Although more research is needed to identify the specific role of the endocannabinoid system in human cognition and the effect that cannabis has on this system and associated mental functions, the studies presented in the current thesis contribute to a better understanding of the various cognitive consequences of using cannabis.

References

Abdullaev Y, Posner MI, Nunnally R, Dishion TJ (2010) Functional MRI evidence for inefficient attentional control in adolescent chronic cannabis abuse. Behavioural Brain Research 215:45-57.

Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL (2007) Vaporization as a smokeless cannabis delivery system: a pilot study. Clinical Pharmacology and Therapeutics 82:572-578.

Akbari Chermahini S, Hickendorff M, Hommel B (2012) Development and validity of a Dutch version of the Remote Associates Task: an item-response theory approach. Thinking Skills and Creativity 7:177-186.

Akbari Chermahini S, Hommel B (2010) The (b)link between creativity and dopamine: spontaneous eye blink rates predict and dissociate divergent and convergent thinking. Cognition 115:458-465

Barbato G, Ficca G, Muscettola G, Fichele M, Beatrice M, Rinaldi F (2000) Diurnal variation in spontaneous eye-blink rate. Psychiatry Research 93:145-151.

Bar-Haim Y, Lamy D, Pergamin L, Bakermans-Kranenburg MJ, van IJzendoorn MH (2007) Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. Psychological Bulletin 133:1-24.

Baumeister RF, Bratslavsky E, Muraven M, Tice DM (1998) Ego depletion: is the active self a limited resource?. Journal of Personality and Social Psychology 74:1252-1265.

Bergamaschi MM, Queiroz RHC, Chagas MHN, de Oliveira DCG, De Martinis BS, Kapczinski F, Quevedo J, Roesler R, Schröder N, Nardi AE, Martin-Santos R, Hallak JEC, Zuardi AW, Crippa JAS (2011) Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. Neuropsychopharmacology 36:1219-1226.

Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, Nosarti C, O'Carroll C, Seal ML, Allen P, Mehta MA, Stone JM, Tunstall N, Giampietro V, Kapur S, Murray RM, Zuardi AW, Crippa JA, Atakan Z, Mcguire P K (2010) Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 35:764-774.

Bhattacharyya S, Crippa JA, Allen P, Martin-Santos R, Borgwardt S, Fusar-Poli P, Rubia K, Kambeitz J, O'Carroll C, Seal M, Giampietro V, Brammer M, Zuardi AW, Atakan Z, McGuire PK (2012) Induction of psychosis by delta-9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. Archives of General Psychiatry 69:27-36.

Bhattacharyya S, Fusar-Poli P, Borgwardt S, Martin-Santos R, Nosarti C, O'Carroll C, Allen P, Seal ML, Fletcher PC, Crippa JA, Giampietro V, Mechelli A, Atakan Z, McGuire PL (2009) Modulation of mediotemporal and ventrostriatal function in humans by delta-9-tetrahydrocannabinol: a neural basis for the effects of Cannabis sativa on learning and psychosis. Archives of General Psychiatry 66:442-451.

Bisogno T, Hanuš L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I, Moriello AS, Davis JB, Mechoulam R, Di Marzo V (2001) Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. British Journal of Pharmacology 134:845-852.

Block RI, Farinpour R, Braverman K (1992) Acute effects of marijuana on cognition: relationships to chronic effects and smoking techniques. Pharmacology Biochemistry and Behavior 43:907-917.

Bloomfield MAP, Morgan CJA, Egerton A, Kapur S, Curran HV, Howes OD (2014) Dopaminergic function in cannabis users and its relationship to cannabis-induced psychotic symptoms. Biological Psychiatry 75:470-478.

Bloomfield MAP, Morgan CJA, Kapur S, Curran HV, Howes OD (2014) The link between dopamine function and apathy in cannabis users: an [18F]-DOPA PET imaging study. Psychopharmacology 231:2251-2259.

Bogacz R (2007) Optimal decision-making theories: linking neurobiology with behaviour. Trends in Cognitive Sciences 11:118-125.

Bolla KI, Cadet J, London ED (1998) The neuropsychiatry of chronic cocaine abuse. The Journal of Neuropsychiatry & Clinical Neurosciences 10:280-289.

Bonnet U, Specka M, Stratmann U, Ochwadt R, Scherbaum N (2014) Abstinence phenomena of chronic cannabis-addicts prospectively monitored during controlled inpatient detoxification: cannabis withdrawal syndrome and its correlation with delta-9-tetrahydrocannabinol and -metabolites in serum. Drug and Alcohol Dependence 143:189-197.

Borgwardt S, Allen P, Bhattacharyya S, Fusar-Poli P, Crippa JA, Seal ML, Fraccaro V, Atakan Z, Martin-Santos R, O'Carroll C, Rubia K, McGuire PK (2008) Neural basis of delta-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition. Biological Psychiatry 64:966-973.

Bossong MG, Mehta MA, van Berckel BNM, Howes OD, Kahn RS, Stokes PRA (2015) Further human evidence for striatal dopamine release induced by administration of delta-9-tetrahydrocannabinol (THC): selectivity to limbic striatum. Psychopharmacology 232:2723-2729.

Bossong MG, van Berckel BNM, Boellaard R, Zuurman L, Schuit RC, Windhorst AD, van Gerven JMA, Ramsey NF, Lammertsma AA, Kahn RS (2009) Delta 9-tetrahydrocannabinol induces dopamine release in the human striatum. Neuropsychopharmacology 34:759-766.

Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD (2001) Conflict monitoring and cognitive control. Psychological Review 108:624-652.

Bourassa M, Vaugeois P (2001) Effects of marijuana use on divergent thinking. Creativity Research Journal 13:411-416.

Bush G, Luu P, Posner MI (2000) Cognitive and emotional influences in anterior cingulate cortex. Trends in Cognitive Sciences 4:215-222.

Bush G, Whalen PJ, Rosen BR, Jenike MA, McInerney SC, Rauch SL (1998) The counting Stroop: an interference task specialized for functional neuroimaging: validation study with functional MRI. Human Brain Mapping 6:270-282.

Campos AC, Guimarães FS (2008) Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. Psychopharmacology 199:223-230.

Carey SE, Nestor L, Jones J, Garavan H, Hester R (2015) Impaired learning from errors in cannabis users: dorsal anterior cingulate cortex and hippocampus hypoactivity. Drug and Alcohol Dependence 155:175-182.

Carter CS, Mintun M, Cohen JD (1995) Interference and facilitation effects during selective attention: an H215O PET study of Stroop task performance. NeuroImage 2:264-272.

Casey BJ, Trainor RJ, Orendi JL, Schubert AB, Nystrom LE, Giedd JN, Castellanos FX, Haxby JV, Noll DC, Cohen JD, Forman SD, Dahl RE, Rapoport JL (1997) A developmental functional MRI study of prefrontal activation during performance of a go-no-go task. Journal of Cognitive Neuroscience 9:835-847.

Colzato LS, Hommel B (2008) Cannabis, cocaine, and visuomotor integration: evidence for a role of dopamine D1 receptors in binding perception and action. Neuropsychologia 46:1570-1575.

Colzato LS, Ozturk A, Hommel B (2012) Meditate to create: the impact of focused-attention and open-monitoring training on convergent and divergent thinking. Frontiers in Psychology 3:116.

Colzato LS, Szapora A, Pannekoek JN, Hommel B (2013) The impact of physical exercise on convergent and divergent thinking. Frontiers in Human Neuroscience 7:824.

Colzato LS, van den Wildenberg WPM, Hommel B (2008) Reduced spontaneous

eye blink rates in recreational cocaine users: evidence for dopaminergic hypoactivity. PLoS ONE 3:e3461.

Colzato LS, Waszak F, Nieuwenhuis S, Posthuma D, Hommel B (2010) The flexible mind is associated with the catechol-O-methyltransferase (COMT) Val158Met polymorphism: evidence for a role of dopamine in the control of task-switching. Neuropsychologia 48:2764-2768.

Cools R, D'Esposito M (2011) Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biological Psychiatry 69:e113-e125.

Cools R, Frank MJ, Gibbs SE, Miyakawa A, Jagust W, D'Esposito M (2009) Striatal dopamine predicts outcome-specific reversal learning and its sensitivity to dopaminergic drug administration. Journal of Neuroscience 29:1538-1543.

Crane NA, Schuster RM, Gonzalez R (2013) Preliminary evidence for a sex-specific relationship between amount of cannabis use and neurocognitive performance in young adult cannabis users. Journal of the International Neuropsychological Society 19:1009-1015.

Crippa JA, Derenusson GN, Ferrari TB, Wichert-Ana L, Duran FL, Martin-Santos R, Simoes MV, Bhattacharyya S, Fusar-Poli P, Atakan Z, Filho AS, Freitas-Ferrari MC, McGuire PK, Zuardi AW, Busatto GF, Hallak JEC (2011) Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. Journal of Psychopharmacology 25:121-130.

Crippa JA, Zuardi AW, Garrido GE, Wichert-Ana L, Guarnieri R, Ferrari L, Azevedo-Marques PM, Hallak JEC, McGuire PK, Busatto GF (2004) Effects of cannabidiol (CBD) on regional cerebral blood flow. Neuropsychopharmacology 29:417-426.

Curran HV, Brignell C, Fletcher S, Middleton P, Henry J (2002) Cognitive and subjective dose-response effects of acute oral delta-9-tetrahydrocannabinol (THC) in infrequent cannabis users. Psychopharmacology (Berl) 164:61-70.

Curran HV, Morgan CJA (2014) Desired and undesired effects of cannabis on the human mind and psychological well-being. In: Handbook of Cannabis, 1st ed. (Pertwee R, ed). Oxford: Oxford University Press.

de Bruijn ERA, Hulstijn W, Verkes RJ, Ruigt GSF, Sabbe BGC (2004) Drug-induced stimulation and suppression of action monitoring in healthy volunteers. Psychopharmacology 177:151-160.

de Bruijn ERA, Sabbe BGC, Hulstijn W, Ruigt GSF, Verkes RJ (2006) Effects of

antipsychotic and antidepressant drugs on action monitoring in healthy volunteers. Brain Research 1105:122-129.

De Dreu CKW, Baas M, Nijstad BA (2008) Hedonic tone and activation level in the mood-creativity link: toward a dual pathway to creativity model. Journal of Personality and Social Psychology 94:739-756.

De Dreu CKW, Nijstad BA, Baas M, Wolsink I, Roskes M (2012) Working memory benefits creative insight, musical improvisation, and original ideation through maintained task-focused attention. Personality and Social Psychology Bulletin 38:656-669.

Debener S, Ullsperger M, Siegel M, Fiehler K, von Cramon DY, Engel AK (2005) Trial-by-trial coupling of concurrent electroencephalogram and functional magnetic resonance imaging identifies the dynamics of performance monitoring. Journal of Neuroscience 25:11730-11737.

Deuschel G, Goddemeier C (1998) Spontaneous and reflex activity of facial muscles in dystonia, Parkinson's disease, and in normal subjects. Journal of Neurology, Neurosurgery & Psychiatry 64:320-324.

Devane WA, Dysarz FA, Johnson MR, Melvin LS, Howlett AC (1988) Determination and characterization of a cannabinoid receptor in rat brain. Molecular Pharmacology 34:605-613.

Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R (1992) Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 258:1946-1949.

Dreisbach G, Müller J, Goschke T, Strobel A, Schulze K, Lesch KP, Brocke B (2005) Dopamine and cognitive control: the influence of spontaneous eyeblink rate and dopamine gene polymorphisms on perseveration and distractibility. Behavioral Neuroscience 119:483-490.

D'Souza DC, Fridberg DJ, Skosnik PD, Williams A, Roach B, Singh N, Carbuto M, Elander J, Schnakenberg A, Pittman B, Sewell RA, Ranganathan M, Mathalon D (2012) Dose-related modulation of event-related potentials to novel and target stimuli by intravenous delta-9-THC in humans. Neuropsychopharmacology 37:1632-1646.

D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, Braley G, Gueorguieva R, Krystal JH (2004) The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology 29:1558-1572.

D'Souza DC, Ranganathan M, Braley G, Gueorguieva R, Zimolo Z, Cooper T, Perry E, Krystal JH (2008) Blunted psychotomimetic and amnestic effects

of delta-9-tetrahydrocannabinol in frequent users of cannabis. Neuropsychopharmacology 33:2505-2516.

Dutilh G, van Ravenzwaaij D, Nieuwenhuis S, van der Maas HLJ, Forstmann BU, Wagenmakers EJ (2012) How to measure post-error slowing: a confound and a simple solution. Journal of Mathematical Psychology 56:208-216.

Earleywine M (2002) Understanding marijuana. Oxford: Oxford University Press.

ElSohly M, Gul W (2014) Constituents of Cannabis sativa. In: Handbook of Cannabis, 1st ed. (Pertwee R, ed). Oxford: Oxford University Press.

Endrass T, Franke C, Kathmann N (2005) Error awareness in a saccade countermanding task. Journal of Psychophysiology 19:275-280.

Eriksen BA, Eriksen CW (1974) Effects of noise letters upon the identification of a target letter in a nonsearch task. Perception & Psychophysics 16:143-149.

Falkenstein M, Hohnsbein J, Hoormann J, Blanke L (1990) Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In: Psychophysiological Brain Research, 1st ed. (Brunia C, Gaillard A, Kok A, ed), pp 192-195. Tilburg: Tilburg University Press.

Falkenstein M, Hoormann J, Christ S, Hohnsbein J (2000) ERP components on reaction errors and their functional significance: a tutorial. Biological Psychology 51:87-107.

Fattore L, Melis M, Fadda P, Pistis M, Fratta W (2010) The endocannabinoid system and nondrug rewarding behaviours. Experimental Neurology 224:23-36.

Fernández-Ruiz J, Hernández M, Ramos JA (2010) Cannabinoid-dopamine interaction in the pathophysiology and treatment of CNS disorders. CNS Neuroscience & Therapeutics 16:e72-e91.

Freed W (1980) Eye-blink rates and platelet monoamine oxidase activity in chronic schizophrenic patients. Biological Psychiatry 15:329-332.

Fridberg DJ, Skosnik PD, Hetrick WP, O'Donnell BF (2013) Neural correlates of performance monitoring in chronic cannabis users and cannabis-naive controls. Journal of Psychopharmacology 27:515-525.

Friendly M (2014) Power. Power analysis for ANOVA designs Available at: http://www.math.yorku.ca/scs/online/power [Accessed February 26, 2015].

Fusar-Poli P, Allen P, Bhattacharyya S, Crippa JA, Mechelli A, Borgwardt S, Martin-Santos R, Seal ML, O'Carrol C, Atakan Z, Zuardi AW, McGuire PK (2010) Modulation of effective connectivity during emotional processing by Δ9-tetrahydrocannabinol and cannabidiol. The International Journal of Neuropsychopharmacology 13:421-432.

Fusar-Poli P, Crippa JA, Bhattacharyya S, Borgwardt S, Allen P, Martin-Santos R, Seal ML, Surguladze SA, O'Carrol C, Atakan Z, Zuardi AW, McGuire PK (2009) Distinct effects of delta-9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Archives of General Psychiatry 66:95-105.

Gaoni Y, Mechoulam R (1964) Isolation, structure and partial synthesis of an active constituent of hashish. Journal of the American Chemical Society 86:1646-1647.

Gehring WJ, Goss B, Coles MGH, Meyer DE, Donchin E (1993) A neural system for error detection and compensation. Psychological Science 4:385-390.

Gerdeman GL, Partridge JG, Lupica CR, Lovinger DM (2003) It could be habit forming: drugs of abuse and striatal synaptic plasticity. Trends in Neurosciences 26:184-192.

Gomes FV, Resstel LBM, Guimarães FS (2011) The anxiolytic-like effects of cannabidiol injected into the bed nucleus of the stria terminalis are mediated by 5-HT1A receptors. Psychopharmacology 213:465-473.

Gratton G, Coles MGH, Donchin E (1983) A new method for off-line removal of ocular artifact. Electroencephalography and Clinical Neurophysiology 55:468-484.

Green B, Kavanagh D, Young R (2003) Being stoned: a review of self-reported cannabis effects. Drug and Alcohol Review 22:453-460.

Grotenhermen F (2003) Pharmacokinetics and pharmacodynamics of cannabinoids. Clinical Pharmacokinetics 42:327-360.

Guilford JP (1967) The nature of human intelligence. New York: McGraw-Hill.

Hallak JEC, Machado-de-Sousa JP, Crippa JA, Sanches RF, Trzesniak C, Chaves C, Bernardo SA, Regalo SC, Zuardi AW (2010) Performance of schizophrenic patients in the Stroop Color Word Test and electrodermal responsiveness after acute administration of cannabidiol (CBD). Revista Brasileira de Psiquiatria 32:56-61.

Harding IH, Solowij N, Harrison BJ, Takagi M, Lorenzetti V, Lubman DI, Seal ML, Pantelis C, Yücel M (2012) Functional connectivity in brain networks underlying cognitive control in chronic cannabis users. Neuropsychopharmacology 37:1923-1933.

Hardwick S, King LA (2008) Home office cannabis potency study. Home Office Scientific Development Branch.

Hart CL, Ilan AB, Gevins A, Gunderson EW, Role K, Colley JA, Foltin RW (2010) Neurophysiological and cognitive effects of smoked marijuana in frequent users. Pharmacology Biochemistry and Behavior 96:333-341.

Hart CL, van Gorp W, Haney M, Foltin RW, Fischman MW (2001) Effects of acute smoked marijuana on complex cognitive performance. Neuropsychopharmacology 25:757-765.

Hazekamp A, Ruhaak R, Zuurman L, van Gerven JMA, Verpoorte R (2006) Evaluation of a vaporizing device (Volcano®) for the pulmonary administration of tetrahydrocannabinol. Journal of Pharmaceutical Sciences 95:1308-1317.

Herrmann MJ, Römmler J, Ehlis AC, Heidrich A, Fallgatter AJ (2004) Source localization (LORETA) of the error-related-negativity (ERN/Ne) and positivity (Pe). Cognitive Brain Research 20:294-299.

Hester R, Nestor L, Garavan H (2009) Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users. Neuropsychopharmacology 34:2450-2458.

Hindocha C, Freeman TP, Schafer G, Gardener C, Das RK, Morgan CJ, Curran HV (2015) Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: A randomised, double-blind, placebo-controlled study in cannabis users. European Neuropsychopharmacology 25:325-334.

Hirvonen J, Goodwin RS, Li CT, Terry GE, Zoghbi SS, Morse C, Pike VW, Volkow ND, Huestis MA, Innis RB (2012) Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. Molecular Psychiatry 17:642-649.

Ho BC, Wassink TH, Ziebell S, Andreasen NC (2011) Cannabinoid receptor 1 gene polymorphisms and marijuana misuse interactions on white matter and cognitive deficits in schizophrenia. Schizophrenia Research 128:66-75.

Hoffman AF, Oz M, Caulder T, Lupica CR (2003) Functional tolerance and blockade of long-term depression at synapses in the nucleus accumbens after chronic cannabinoid exposure. Journal of Neuroscience 23:4815-4820.

Holroyd CB, Coles MGH (2002) The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. Psychological Review 109:679-709.

Hommel B (2012) Convergent and divergent operations in cognitive search. In: Cognitive search: evolution, algorithms, and the brain, 1st ed. (Todd P, Hills T, Robbins T, ed), pp 221-235. Cambridge, MA: MIT Press.

Hunault CC, Böcker KBE, Stellato RK, Kenemans JL, de Vries I, Meulenbelt J (2014) Acute subjective effects after smoking joints containing up to 69 mg delta-9-tetrahydrocannabinol in recreational users: a randomized, crossover clinical trial. Psychopharmacology 231:4723-4733.

Inzlicht M, Schmeichel BJ (2012) What is ego depletion? Toward a mechanistic revision of the resource model of self-control. Perspectives on Psychological Science 7:450-463.

Kalivas PW, Volkow ND (2005) The neural basis of addiction: a pathology of motivation and choice. American Journal of Psychiatry 162:1403-1413.

Karson CN (1983) Spontaneous eye-blink rates and dopaminergic systems. Brain 106:643-653.

Kawashima R, Satoh K, Itoh H, Ono S, Furumoto S, Gotoh R, Koyama M, Yoshioka S, Takahashi T, Takahashi K, Yanagisawa T, Fukuda H (1996) Functional anatomy of go/no-go discrimination and response selection: a PET study in man. Brain Research 728:79-89.

Kelleher LM, Stough C, Sergejew AA, Rolfe T (2004) The effects of cannabis on information-processing speed. Addictive Behaviors 29:1213-1219.

Kleven MS, Koek W (1996) Differential effects of direct and indirect dopamine agonists on eye blink rate in cynomolgus monkeys. Journal of Pharmacology and Experimental Therapeutics 279:1211-1219.

Kowal MA, Colzato LS, Hommel B (2011) Decreased spontaneous eye blink rates in chronic cannabis users: evidence for striatal cannabinoid-dopamine interactions. PLoS ONE 6:e26662.

Kowal MA, Hazekamp A, Colzato LS, van Steenbergen H, van der Wee NJA, Durieux J, Manai M, Hommel B (2015) Cannabis and creativity: highly potent cannabis impairs divergent thinking in regular cannabis users. Psychopharmacology 232:1123-1134.

Kowal MA, Hazekamp A, Colzato LS, van Steenbergen H, Hommel B (2013) Modulation of cognitive and emotional processing by cannabidiol: the role of the anterior cingulate cortex. Frontiers in Human Neuroscience 7.

Kowal M, van Steenbergen H, Colzato LS, Hazekamp A, van der Wee NJA, Manai M, Durieux J, Hommel B (2015) Dose-dependent effects of cannabis on the neural correlates of error monitoring in frequent cannabis users. European Neuropsychopharmacology 25:1943-1953.

Kuepper R, Ceccarini J, Lataster J, van Os J, van Kroonenburgh M, van Gerven JMA, Marcelis M, Van Laere K, Henquet C (2013) Delta-9-tetrahydrocannabinol-induced dopamine release as a function of psychosis risk: 18F-fallypride positron emission tomography study. PLoS ONE 8:e70378.

Kuepper R, Morrison PD, van Os J, Murray RM, Kenis G, Henquet C (2010) Does dopamine mediate the psychosis-inducing effects of cannabis? A review and integration of findings across disciplines. Schizophrenia Research

121:107-117.
Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Harnett Sheehan K, Janavs J, Dunbar G (1997) The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. European Psychiatry 12:224-231.
Luo X, Zhang S, Hu S, Bednarski SR, Erdman E, Farr OM, Hong KI, Sinha R, Mazure CM, Li CSR (2013) Error processing and gender-shared and -specific neural predictors of relapse in cocaine dependence. Brain 136:1231-1244.
Marco E, Garcia-Gutierrez MS, Bermudez-Silva FJ, Moreira FA, Guimarães FS, Manzanares J, Viveros MP (2011) Endocannabinoid system and psychiatry: in search of a neurobiological basis for detrimental and potential therapeutic effects. Frontiers in Behavioral Neuroscience 5:63.
Marhe R, Luijten M, van de Wetering BJM, Smits M, Franken IHA (2013) Individual differences in anterior cingulate activation associated with attentional bias predict cocaine use after treatment. Neuropsychopharmacology 38:1085-1093.
Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI (1990) Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 346:561-564.
McDonald J, Schleifer L, Richards JB, de Wit H (2003) Effects of THC on behavioral measures of impulsivity in humans. Neuropsychopharmacology 28:1356-1365.
McPartland J, Russo E (2014) Non-phytocannabinoid constituents of cannabis and herbal synergy. In: Handbook of Cannabis, 1st ed. (Pertwee R, ed). Oxford: Oxford University Press.
Mechoulam R, Parker LA, Gallily R (2002) Cannabidiol: an overview of some pharmacological aspects. Journal of Clinical Pharmacology 42:11-19.
Mednick S (1962) The associative basis of the creative process. Psychological Review 69:220-232.
Mink JW (1996) The basal ganglia: focused selection and inhibition of competing motor programs. Progress in Neurobiology 50:381-425.
Mizrahi R, Suridjan I, Kenk M, George TP, Wilson A, Houle S, Rusjan P (2013) Dopamine response to psychosocial stress in chronic cannabis users: a PET study with [11C]-(+)-PHNO. Neuropsychopharmacology 38:673-682.
Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G (2007) Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. The Lancet 370:319-328.

Morgan CJA, Freeman TP, Schafer GL, Curran HV (2010) Cannabidiol attenuates the appetitive effects of delta-9-tetrahydrocannabinol in humans smoking their chosen cannabis. Neuropsychopharmacology 35:1879-1885.

Morgan CJA, Gardener C, Schafer G, Swan S, Demarchi C, Freeman TP, Warrington P, Rupasinghe I, Ramoutar A, Tan N, Wingham G, Lewis S, Curran HV (2012) Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being. Psychological Medicine 42:391-400.

Morgan CJA, Schafer G, Freeman TP, Curran HV (2010) Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study. The British Journal of Psychiatry 197:285-290.

Murphy PR, Robertson IH, Allen D, Hester R, O'Connell RG (2012) An electrophysiological signal that precisely tracks the emergence of error awareness. Frontiers in Human Neuroscience 6:65.

Nicholls C, Bruno R, Matthews A (2015) Chronic cannabis use and ERP correlates of visual selective attention during the performance of a flanker go/nogo task. Biological Psychology 110:115-125.

Nieuwenhuis S, Ridderinkhof KR, Blom J, Band GPH, Kok A (2001) Error-related brain potentials are differentially related to awareness of response errors: evidence from an antisaccade task. Psychophysiology 38:752-760.

Nijstad BA, De Dreu CKW, Rietzschel EF, Baas M (2010) The dual pathway to creativity model: creative ideation as a function of flexibility and persistence. European Review of Social Psychology 21:34-77.

Pardo JV, Pardo PJ, Janer KW, Raichle ME (1990) The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. Proceedings of the National Academy of Sciences 87:256-259.

Paus T (2001) Primate anterior cingulate cortex: where motor control, drive and cognition interface. Nature Reviews Neuroscience 2:417-424.

Pertwee RG (2008) The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta-9-tetrahydrocannabinol, cannabidiol and delta-9-tetrahydrocannabivarin. The British Journal of Pharmacology 153:199-215.

Quik M, Chen L, Parameswaran N, Xie X, Langston JW, McCallum SE (2006) Chronic oral nicotine normalizes dopaminergic function and synaptic plasticity in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned primates. The Journal of Neuroscience 26:4681-4689.

Rabbitt PMA (1966) Errors and error correction in choice-response tasks. Journal

of Experimental Psychology 71:264-272.
Ramaekers JG, Kauert G, Theunissen EL, Toennes SW, Moeller MR (2008) Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. Journal of Psychopharmacology 23:266-277.
Ramaekers JG, Kauert G, van Ruitenbeek P, Theunissen EL, Schneider E, Moeller MR (2006) High-potency marijuana impairs executive function and inhibitory motor control. Neuropsychopharmacology 31:2296-2303.
Raven JC, Court JH, Raven J (1988) Manual for Raven's progressive matrices and vocabulary scales. London: Lewis.
Runco MA (2007) Creativity: theories, themes, and issues. San Diego, CA: Academic Press.
Russell JA, Weiss A, Mendelsohn GA (1989) Affect grid: a single-item scale of pleasure and arousal. Journal of Personality and Social Psychology 57:493-502.
Russo EB (2011) Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. British Journal of Pharmacology 163:1344-1364.
Schafer GL, Feilding A, Morgan CJA, Agathangelou M, Freeman TP, Curran HV (2012) Investigating the interaction between schizotypy, divergent thinking and cannabis use. Consciousness and Cognition 21:292-298.
Schier ARM, Ribeiro NPO, Silva ACO, Hallak JEC, Crippa JA, Nardi AE, Zuardi AW (2012) Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug. Revista Brasileira de Psiquiatria 34:104-117.
Schoedel KA, Harrison SJ (2012) Subjective and physiological effects of oromucosal sprays containing cannabinoids (nabiximols): potentials and limitations for psychosis research. Current Pharmaceutical Design 18:5008-5014.
Schubart CD, Sommer IE, van Gastel WA, Goetgebuer RL, Kahn RS, Boks MP (2011) Cannabis with high cannabidiol content is associated with fewer psychotic experiences. Schizophrenia Research 130:216-221.
Schulz S, Arning L, Pinnow M, Wascher E, Epplen JT, Beste C (2012) When control fails: influence of the prefrontal but not striatal dopaminergic system on behavioural flexibility in a change detection task. Neuropharmacology 62:1028-1033.
Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK (2007) Individual differences in reward responding explain placebo-induced expectations and effects. Neuron 55:325-336.
Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK (2008)

Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. Archives of General Psychiatry 65:220-231.
Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ (2011) The integration of negative affect, pain and cognitive control in the cingulate cortex. Nature Reviews Neuroscience 12:154-167.
Shou-Zhong Y (1997) The divine farmer's materia medica: a translation of the Shen Nong Ben Cao Jing. Boulder, CO: Blue Poppy Press.
Shukla D (1985) Blink rate as clinical indicator. Neurology 35:286.
Spronk D, Dumont GJH, Verkes RJ, de Bruijn ERA (2011) Acute effects of delta-9-tetrahydrocannabinol on performance monitoring in healthy volunteers. Frontiers in Behavioral Neuroscience 5:59.
Stadelmann AM, Juckel G, Arning L, Gallinat J, Epplen JT, Roser P (2011) Association between a cannabinoid receptor gene (CNR1) polymorphism and cannabinoid-induced alterations of the auditory event-related P300 potential. Neuroscience Letters 496:60-64.
Stemmer B, Segalowitz SJ, Witzke W, Schönle PW (2004) Error detection in patients with lesions to the medial prefrontal cortex: an ERP study. Neuropsychologia 42:118-130.
Stokes PR, Egerton A, Watson B, Reid A, Lappin J, Howes OD, Nutt DJ, Lingford-Hughes AR (2012) History of cannabis use is not associated with alterations in striatal dopamine D2/D3 receptor availability. Journal of Psychopharmacology 26:144-149.
Stokes PR, Mehta MA, Curran HV, Breen G, Grasby PM (2009) Can recreational doses of THC produce significant dopamine release in the human striatum?. NeuroImage 48:186-190.
Tapert SF, Schweinsburg AD, Drummond SPA, Paulus MP, Brown SA, Yang TT, Frank LR (2007) Functional MRI of inhibitory processing in abstinent adolescent marijuana users. Psychopharmacology 194:173-183.
Tart CT (1970) Marijuana intoxication: common experiences. Nature 226:701-704.
Taylor JR, Elsworth JD, Lawrence MS, Sladek JR, Roth RH, Redmond DE (1999) Spontaneous blink rates correlate with dopamine levels in the caudate nucleus of MPTP-treated monkeys. Experimental Neurology 158:214-220.
Theunissen EL, Kauert GF, Toennes SW, Moeller MR, Sambeth A, Blanchard MM, Ramaekers JG (2012) Neurophysiological functioning of occasional and heavy cannabis users during THC intoxication. Psychopharmacology 220:341-350.
Tinklenberg JR, Darley CF, Roth WT, Pfefferbaum A, Kopell BS (1978) Marijuana effects on associations to novel stimuli. The Journal of Nervous

and Mental Disease 166:362-364.

Torrance EP (1966) Torrance tests of creative thinking-norms. Lexington, MA: Personal Press.

Ullsperger M, Fischer AG, Nigbur R, Endrass T (2014) Neural mechanisms and temporal dynamics of performance monitoring. Trends in Cognitive Sciences 18:259-267.

Urban NBL, Slifstein M, Thompson JL, Xu X, Girgis RR, Raheja S, Haney M, Abi-Dargham A (2012) Dopamine release in chronic cannabis users: a [11c]raclopride positron emission tomography study. Biological Psychiatry 71:677-683.

Volkow ND, Wang GJ, Telang F, Fowler JS, Alexoff D, Logan J, Jayne M, Wong C, Tomasi D (2014) Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. Proceedings of the National Academy of Sciences 111:E3149-E3156.

Weckowicz TE, Fedora O, Mason J, Radstaak D, Bay KS, Yonge KA (1975) Effect of marijuana on divergent and convergent production cognitive tests. Journal of Abnormal Psychology 84:386-398.

Yeung N, Botvinick MM, Cohen JD (2004) The neural basis of error detection: conflict monitoring and the error-related negativity. Psychological Review 111:931-959.

Zanelati TV, Biojone C, Moreira FA, Guimarães FS, Joca SRL (2010) Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. British Journal of Pharmacology 159:122-128.

Zenasni F, Lubart T (2011) Pleasantness of creative tasks and creative performance. Thinking Skills and Creativity 6:49-56.

Zuardi AW, Cosme RA, Graeff FG, Guimarães FS (1993) Effects of ipsapirone and cannabidiol on human experimental anxiety. Journal of Psychopharmacology 7:82-88.

Zuardi AW, Crippa JA, Hallak JEC, Pinto JP, Chagas MHN, Rodrigues GGR, Dursun SM, Tumas V (2009) Cannabidiol for the treatment of psychosis in Parkinson's disease. Journal of Psychopharmacology 23:979-983.

Zuardi AW, Hallak JEC, Dursun SM, Morais SL, Sanches RF, Musty RE, Crippa JA (2006) Cannabidiol monotherapy for treatment-resistant schizophrenia. Journal of Psychopharmacology 20:683-686.

Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG (1982) Action of cannabidiol on the anxiety and other effects produced by delta-9-THC in normal subjects. Psychopharmacology 76:245-250.

Zuurman L, Roy C, Schoemaker RC, Hazekamp A, den Hartigh J, Bender JC,

Verpoorte R, Pinquier JL, Cohen AF, van Gerven JMA (2008) Effect of intrapulmonary tetrahydrocannabinol administration in humans. Journal of Psychopharmacology 22:707-716.

Nederlandse Samenvatting

Samenvatting en algemene discussie

In dit proefschrift onderzoeken we zowel de acute als de chronische effecten van cannabis op de mechanismen die ten grondslag liggen aan cognitieve functies, in een populatie van regelmatige gebruikers van cannabis. We voerden experimenten uit met als doel de impact te bepalen van cannabis op dopamine-gerelateerde functies, creatieve processen en *error monitoring* in het brein. Daarnaast voerden we een literatuur review uit naar de effecten van cannabidiol (CBD) op emotionele en cognitieve processen.

Ten eerste suggereren onze experimenten, zoals beschreven in hoofdstuk 2, dat lange-termijngebruik van cannabis een schadelijk effect heeft op het dopaminerge functioneren van het striatum. Metingen van de spontane oogknipper-frequentie (eye blink rate, EBR; een klinische marker voor striatale dopamine (DA) transmissie; Karson, 1983; Shukla, 1985; Taylor et al., 1999) onder regelmatige cannabisgebruikers liet een significant verschil zien ten opzichte van een controlegroep bestaande uit niet-gebruikers met vergelijkbare demografische karakteristieken. De cannabisgebruikers toonden een duidelijke afname van EBR, in vergelijking met de controlegroep. Deze resultaten suggereren dat chronisch cannabisgebruik een verstorend effect heeft op de dopaminerge transmissie in het striatum. Dit gebeurt mogelijk indirect door complexe interacties met het endocannabinoidsysteem (Hoffman et al., 2003; Fattore et al., 2010; Fernández-Ruiz et al., 2010).

Ten tweede toont dit proefschrift, in hoofdstuk 3, hoe regelmatige cannabisgebruikers verstoord *divergent thinking performance* vertonen na toediening van een hoge dosis delta-9-tetrahydrocannabinol (THC; 22 mg) in de vorm van verdampte cannabis, in verhouding tot een toediening van een lage dosis THC (5.5 mg) of een placebo. Divergent denken vind plaats wanneer men probeert om zoveel mogelijk antwoorden te formuleren op een vraag zonder duidelijke definitie (ook wel bekend als 'brainstormen'). Dit wordt beschouwd als een mentaal proces dat cruciaal is voor creatieve prestaties (Guilford, 1967) en is waarschijnlijk gelinkt aan het functioneren van DA in het striatum (Akbari Chermahini and Hommel, 2010). Hoewel we in eerste instantie dachten dat de verstoorde creatieve prestatie van onze studiepersonen een mogelijk gevolg was van geïnduceerde afleiding van de geest door verminderde DA spiegels in het striatum (Cools and D'Esposito, 2011), lijkt deze verklaring minder waarschijnlijk in het licht van meer recente bevindingen over DA en THC (Bossong et al., 2015). Toekomstig neuro-imaging onderzoek kan ons helpen om beter te begrijpen welke neurale mechanismen betrokken zijn bij de

effecten van cannabinoiden op divergent denken en verwante creatieve processen. Het is zeker de moeite waard om verder te kijken naar de verhouding tussen cannabis en creativiteit, gezien het wijdverbreide geloof dat cannabis werkt als inspiratiebron voor creativiteit (e.g. Green et al., 2005). Wellicht zou het introduceren van een motiverende factor aan de studieopzet kunnen bijdragen aan een hogere relevantie van de studieresultaten; wanneer een cannabisgebruiker een creatieve taak als persoonlijk relevant beschouwd, dan is het waarschijnlijk dat de resultaten van die taak een realistischer representatie geven van de creatieve performance van die persoon buiten de studieopzet. Dit is dan meer in lijn met anekdotische verhalen van cannabisgebruikers, die claimen dat het gebruik van cannabis als verbeteraar van creativiteit met name werkt in situaties die ze persoonlijk plezierig vinden.

In de derde plaats toont ons onderzoek, volgens de resultaten in hoofdstuk 4, een dosis-afhankelijk effect van verdampte cannabis op de neurale correlaten van *error monitoring* bij chronische cannabisgebruikers. Er kon worden aangetoond dat twee *event-related potentials* (ERPs) die gerelateerd zijn aan het herkennen van discrepanties tussen verwachte en uitgevoerde acties – namelijk de *error-related negativity* (ERN) en *error positivity* (Pe) – verschillend werden beïnvloed door de THC doses die werden toegediend in de studie. Zo leidde de hoge THC dosis (22 mg) tot een vermindering van ERN en Pe amplitude in vergelijking met placebo, terwijl een lage dosis THC (5.5 mg) resulteerde in alleen een vermindering van Pe amplitude, ten opzichte van placebo. Er is bewijs dat de ERN en Pe verschillende neurale processen vertegenwoordigen die betrokken zijn bij het monitoren van fouten maken (Nieuwenhuis et al., 2001) en dat de Pe betrokken is bij het bewust ervaren van fouten (Nieuwenhuis et al., 2001, Endrass et al., 2005; Murphy et al., 2012). Op basis hiervan stellen wij voor dat een hoge dosis cannabis een invloed heeft op zowel het initiële automatische (onbewuste) proces van verwerken van fouten, als ook op de latere (en bewuste) fases van foutverwerking. De lage dosis THC, daarentegen, beïnvloed enkel de bewuste, late, herkenning van de discrepantie tussen de verwachte en de uitgevoerde actie. Om deze aannames verder te bevestigen moet aanvullend onderzoek worden gedaan waarbij gedrag bij proefpersonen meer uitvoerig wordt bestudeerd naar deze aspecten. Goede aanvullende informatie zou kunnen worden verkregen door een studieopzet waarbij het meten van ERPs wordt gecombineerd met een manuele respons die de bewustheid kan meten voor het begaan van een fout door het studieobject.

In de vierde plaats (hoofdstuk 5) geeft dit proefschrift een overzicht van alle beschikbare wetenschappelijke literatuur in de vorm van een review over

neuro-imaging onderzoek betreffende de effecten van CBD op affectieve en cognitieve *processing*. In deze review komt er een belangrijke rol naar voren voor de *antrior cingulate cortex* (ACC). De resultaten van de besproken studies spreken elkaar tegen: CBD lijkt de activiteit van de ACC te kunnen verminderen (Fusar-Poli et al., 2009; Fusar-Poli et al., 2010), heeft geen effect (Borgwardt et al., 2008; Bhattacharyya et al., 2009; Bhattacharyya et al., 2010), of kan ACC activiteit juist bevorderen (Bhattacharyya et al., 2010). Hoewel het mechanisme waarop deze effecten plaatsvinden niet bekend is, suggereren we in ons hoofdstuk dat de modulatie van ACC activiteit door CBD kan leiden tot een verbeterde verwerking van fouten vanwege de cruciale rol die de ACC speelt bij dit proces (Bush et al., 2000; Botvinick et al., 2001; Paus, 2001; Shackman et al., 2011) en vanwege het tegengestelde effect van CBD op *executive control* functies, in vergelijking met THC (Bhattacharyya et al., 2010; Morgan et al., 2010, 2012).

Wanneer we de resultaten van hoofdstuk 4 en 5 combineren, dan blijkt het belang om de relatie tussen cannabisgebruik en *error monitoring* verder te bestuderen, en zo de invloed van cannabis op het dagelijks functioneren van subjecten beter te kunnen begrijpen. Gezien het aangetaste vermogen om gedrag aan te passen onder invloed van veranderende omstandigheden en negatieve consequenties een centraal klinisch symptoom is van drugverslaving (Kalivas and Volkow, 2005), en gezien het feit dat een verminderd vermogen om te leren van fouten is gerelateerd aan slechte prognoses bij behandeling van drugverslaving (Luo et al., 2013; Marhe et al., 2013), lijkt het van belang om meer kennis te verzamelen over de effecten van cannabis op iemands vaardigheid om fouten te detecteren en te corrigeren. Dit kan vervolgens helpen bij het opstellen van een effectief behandelprogramma voor drugverslaving. Onderzoek naar de lange-termijn effecten van cannabisgebruik suggereert sterk dat het vermogen tot *error monitoring* bij regelmatige gebruikers van cannabis verstoord is (Tapert et al., 2007; Hester et al., 2009; Falkenstein et al., 2013; Nicholls et al., 2015; Carey et al., 2015). Als gevolg hiervan, en gezien de resultaten van hoofdstuk 4 die aantoonden dat THC-rijke cannabis negatieve invloed kan hebben op het verwerken van fouten, verdient het aanbeveling om verder te kijken naar het verwachtte tegengestelde effect van CBD op dit proces. Afgezien van de mogelijkheid dat CBD direct de door THC veroorzaakte verslechtering zou kunnen tegengaan, is het wellicht nog interessanter om te onderzoeken of het beschermende effect van CBD ook op de lange termijn stand houdt, zoals gesuggereerd door Morgan et al. (2012). Mocht

dit zo zijn, dan ontstaat er een mogelijke therapeutische rol voor CBD bij de behandeling van cannabisverslaving.

Het is de moeite waard om de bevindingen van dit proefschrift verder te evalueren, in het licht van recente nieuwe ontdekkingen. Geavanceerd neuro-imaging onderzoek laat zien dat regelmatig cannabisgebruik bij volwassen niet leidt tot significante verschillen in dopamine D_2/D_3 receptor beschikbaarheid of de aanmaak van dopamine in het striatum (Stokes et al., 2012; Urban et al., 2012; Mizrahi et al., 2013; Volkow et al., 2014). Daar tegenover staat onderzoek van Bloomfield et al. (2014a) waarbij een afgenomen DA synthese capaciteit in het striatum werd gevonden bij cannabisgebruikers, hetgeen de studie in verband brengt met een verminderde gevoeligheid van het beloningsysteem en met verminderde motivatie bij chronische cannabisgebruikers. Bovendien is er gesuggereerd dat de mate van verslechtering van dopaminerge transmissie positief is gecorreleerd met de leeftijd waarop met cannabis consumptie is begonnen (Urban et al., 2012; Bloomfield et al., 2014a). Als gevolg hiervan zijn neuro-imaging studies naar de effecten van regelmatig cannabis gebruik op *dopaminergic functioning* niet doorslaggevend. Vanuit dit perspectief zijn de resultaten van onze eigen studie, hoewel we een robuuste vermindering zagen van EBR in regelmatige cannabisgebruikers, helaas niet volledig eenduidig.

Een recente studie door Bossong et al. (2015) combineert en her-analyseert de gegevens van twee eerdere studies naar de acute effecten van THC toediening op DA transmissie in het striatum (Bossong et al., 2009; Stokes et al., 2009). Daarbij bleek dat de toename van DA afgifte na THC toediening beperkt is, vergeleken bij andere recreatief gebruikte drugs zoals amfetamine of nicotine. Omdat THC toediening leidt tot potente gedragseffecten, suggereren de onderzoekers dat deze overduidelijke effecten van cannabis waarschijnlijk niet alleen veroorzaakt worden door *dopaminergic functioning* van het striatum. Het is ook mogelijk dat de effecten van THC op gedrag op directe wijze gemedieerd worden door het endocannabinoidsysteem, hoewel het exacte mechanisme waardoor dat zou moeten gebeuren nog onduidelijk is (Bossong et al., 2015). Wetenschappelijk onderzoek naar chronische maar ook acute effecten van cannabinoiden op striatale DA wijst in het algemeen op een verstorend effect op het normale functioneren van deze neurotransmitter. Toch is het niet waarschijnlijk dat een verstoring van de dopaminerge werking op langere termijn desastreuze gevolgen heeft. Wellicht is hierbij de leeftijd waarop voor het eerst cannabis is gebruikt een cruciale parameter. Om dit duidelijker te krijgen is meer onderzoek nodig naar de

relatie tussen *dopaminergic functioning* bij chronische cannabis gebruikers en de psychose-inducerende effecten van cannabis (Kuepper et al., 2010).

Samengevat moeten we concluderen dat de mechanismen waarlangs cannabis een invloed heeft op cognitie en verwante neurale functies complex zijn, en slechts deels begrepen. Belangrijke redenen die hiervoor zijn aan te wijzen zijn de farmacologische complexiteit van de cannabis plant zelf, maar ook de wijdverspreide aanwezigheid van het endocannabinoidsysteem in het menselijk lichaam, welke interactie heeft met andere neuromodulaire systemen op allerlei verschillende wijzen. In combinatie met de vele wettelijke restricties die rusten op onderzoek met de verboden drug Cannabis, zorgt dit voor een uiterst complexe situatie waarin het lastig blijft om de effecten van cannabis te onderzoeken, ook op cognitie. We hopen dat toekomstig onderzoek in staat zal zijn om te bepalen welke rol het endocannabinoidsysteem heeft bij menselijke cognitie, en wat voor effect cannabis heeft op dit systeem en de daarmee verbonden mentale functies.

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Curriculum Vitae

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Publications

Articles published:

Kowal MA, Hazekamp A, Grotenhermen F (2016) Review on clinical studies with cannabis and cannabinoids 2010-2014. Cannabinoids 11:1–18

Kowal MA, van Steenbergen H, Colzato LS, Hazekamp A, van der Wee NJA, Manai M, Durieux J, Hommel B (2015b) Dose-dependent effects of cannabis on the neural correlates of error monitoring in frequent cannabis users. European Neuropsychopharmacology 25:1943-1953. DOI: 10.1016/j.euroneuro.2015.08.001

Kowal MA, Hazekamp A, Colzato LS, van Steenbergen H, van der Wee NJA, Durieux J, Manai M, Hommel B (2015a) Cannabis and creativity: highly potent cannabis impairs divergent thinking in regular cannabis users. Psychopharmacology 232:1123-1134. DOI: 10.1007/s00213-014-3749-1

Kowal MA, Hazekamp A, Colzato LS, van Steenbergen H, Hommel B (2013) Modulation of cognitive and emotional processing by cannabidiol: the role of the anterior cingulate cortex. Frontiers in Human Neuroscience 7. DOI: 10.3389/fnhum.2013.0

Kowal MA, Colzato LS, Hommel B (2011) Decreased spontaneous eye blink rates in chronic cannabis users: evidence for striatal cannabinoid-dopamine interactions. PLoS ONE 6:e26662. DOI: 10.1371/journal.pone.0026662