1

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.