Thinking high : the impact of cannabis on human cognition

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Summary and general discussion

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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.