

Epidemiological and biological mechanisms of cannabis as cause of psychosis

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SUMMARY

The use of cannabis has been widely established as a risk factor for psychosis. Yet, the exact nature of the association still remains unclear, including the issue of self-medication or reverse causality. Previously it had been suggested that the link between cannabis and psychosis might best be understood in terms of interaction between genes and environment, where individual vulnerability combines with environmental risk such as cannabis use in causing psychotic disorder. However, it is widely unknown whether cannabis use might also interact with other environmental risk factors. In addition, the biological mechanisms behind such findings remain elusive.

This thesis therefore considered **epidemiological (studied in chapters 2, 3 and 4)** as well as **biological mechanisms (discussed in chapters 5, 6, 7, and 9)** that may underlie the association between exposure to cannabis and the development of psychotic symptoms and schizophrenia.

CHAPTER 1 provides an overview on the epidemiology and etiology of psychotic disorders such as schizophrenia and discusses cannabis use as an important environmental risk factor. Furthermore, epidemiological studies on the link between cannabis use and psychosis are reviewed and an outlook is given on potential biological correlates of this association, concluding that dopamine might play a role in mediating the effects of cannabis on psychosis risk. The chapter subsequently discusses existing findings on differential sensitivity to the effects of cannabis, indicating that genetic predisposition for psychosis as well as variation in specific molecular polymorphisms might give rise to increased vulnerability. Also, cannabidiol is introduced as another cannabinoid and ingredient of cannabis with potential antipsychotic properties. Finally, research gaps in the study of cannabis as cause of psychosis are identified and the aims of the current thesis are outlined.

CHAPTER 2 deals with the temporal association between exposure to cannabis and the development of psychotic symptoms to shed further light on the nature of this association. In addition it was of interest whether cannabis use increases psychosis risk by impacting on the persistence of subclinical psychotic symptoms. For this purpose, data from a large German prospective cohort study of adolescents and young adults (Early Developmental Stages of Psychopathology, EDSP) were analyzed. The following research questions were formulated: i) Does cannabis use precede the onset of incident subclinical psychotic symptoms in adolescence and young adults? And ii) Does cannabis use increase psychosis risk by negatively impacting on the persistence of these subclinical psychotic symptoms? Analyses of the

data revealed that, in individuals who were cannabis naïve at baseline, use of cannabis between baseline and first follow-up was significantly associated with increased risk of incident psychotic symptoms at second follow-up. Moreover it was revealed that continued use of cannabis (i.e. cannabis use at both baseline and first follow-up) increased the risk that subclinical psychotic symptoms persisted throughout the period between first and second follow-up. Together these findings provide further evidence for a causal role of cannabis use in the etiology of psychosis. Moreover, a mechanism of abnormal persistence of subclinical psychotic symptoms is suggested to form part of the pathway from cannabis to psychosis.

CHAPTER 3 considers the possibility of environmental moderation of the cannabis-psychosis relationship. In particular we investigated whether urbanicity – growing up in an urban environment – played a role for the long-term psychosis-inducing effects of cannabis. Again, data from the German EDSP study were analyzed and the interaction between urbanicity and cannabis use at follow-up was calculated. To ensure the prediction of incident psychotic symptoms, all individuals with preexisting psychotic symptoms at baseline were excluded from the analyses. It was revealed that the risk to develop psychotic symptoms following cannabis use was much higher for individuals who grew up in an urban environment compared to individuals from the rural surroundings. This suggests that, in addition to genetic factors, exposure to environmental risk factors may induce increased sensitivity to the psychosis-inducing effects of cannabis.

CHAPTER 4 presents a further epidemiological study on environmental moderation of the cannabis-psychosis relationship. Previous research had indicated that trauma interacts with cannabis use in causing psychosis: Individuals who were exposed to trauma during childhood had a higher risk of developing psychotic symptoms and schizophrenia following cannabis use later in life. The present study aimed at replication of this finding in the large cohort of the prospective German EDSP study. Contrary to our hypothesis and to previous findings, trauma was not associated with increased risk of developing psychotic symptoms after cannabis use.

CHAPTER 5 provides an update on the dopamine dysfunction in psychosis and schizophrenia. This includes neurochemical imaging studies on mechanisms of presynaptic and postsynaptic dopamine function in both striatal and extrastriatal regions of the brain, including prefrontal areas. It is concluded that contrary to the long-standing claim of involvement of mesolimbic dopamine dysregulation, it is rather a dysfunction in nigrostriatal dopaminergic pathways and in particular associative striatum that is associated with (early) expression of symptomatology in psychosis.

In order to elucidate the role of dopamine in the psychosis inducing effects of cannabis, **CHAPTER 6** summarizes and integrates research across different disciplines on the interaction between the dopamine and the endocannabinoid system. Dopamine plays a central role in the emergence as well as experience of psychotic symptoms. Striatal dopaminergic hyperfunction has been implicated in the positive symptoms of psychosis, while dopaminergic hypoactivity in prefrontal brain regions has been assumed to underlie the expression of negative symptoms. Evidence from animal research suggests that endocannabinoids are key components in the regulation of dopaminergic neurotransmission, both in striatal and prefrontal brain regions. Moreover, THC has been shown to differentially affect these pathways. It is concluded that the repeated administration of THC might alter PFC function and impair cognition by acting on dopamine signaling via activation of CB1 receptors. In the ventral tegmental area, it seems that THC leads to burst firing of dopamine neurons and as a consequence increased dopamine levels in the striatum. Here, THC might additionally exert its effects by directly influencing synaptic plasticity. Yet, most of the evidence discussed in this chapter stems from animal research, and research into the processes underlying cannabis-induced psychosis in the human brain is demanded.

In line with the considerations put forward in chapter 6, **CHAPTER 7** tests the hypothesis that THC increases the risk of developing psychotic symptoms by stimulating striatal dopamine neurotransmission. For this purpose, Positron Emission Tomography and [^{18}F] fallypride was used to study ligand displacement at D2 receptors – indicative of increased dopamine release – following pulmonary administration of THC in 9 patients with psychotic disorder, 9 first-degree relatives and 10 healthy controls. Analyses revealed significant dopamine release associated with administration of THC in both patients with psychotic disorder and first-degree relatives. In line with previous findings, no THC-induced dopamine release was found in healthy controls. These findings support a dopaminergic mechanism of cannabis-induced psychosis in individuals at risk for psychosis.

CHAPTER 8 investigates patterns of cannabis use in relation to craving for cannabis in daily life of patients with psychotic disorder and healthy controls. The study makes use of the Experience Sampling Method (ESM), a structured diary technique that pseudo-randomly collects multiple observations per person during several consecutive days. Participants received a digital wrist watch and a paper-and-pencil ESM booklet. Twelve times a day on six consecutive days, the watch emitted a beep at random moments. After each beep, participants were asked to fill in a self-assessment form, collecting reports on craving intensity, severity of symptoms and cannabis use rated on 7-point Likert scales at the moment of the beep. In addition to collecting information on craving levels by means of the ESM booklets, craving was

assessed with the Obsessive Compulsive Drug Use Scale (OCDUS) for cannabis use. It was revealed that patients with psychotic disorder displayed higher levels of craving when measured with the OCDUS, but did not differ from healthy controls in craving intensity when measured in daily life with ESM. Also ESM craving was a better predictor of cannabis use during the ESM week than scores on the OCDUS. Craving in daily life was significantly associated with cannabis use in daily life. Notably, this association was stronger for controls than for patients, suggesting that patients are either prevented more often from use or alternatively use cannabis rather independent from inner cues. In general, no differences were found between patients receiving different types of antipsychotics, yet failure to detect such differences might be due to a lack of power. Overall, the study emphasizes the need to further elucidate the role of craving in relation to cannabis use in patients with psychosis, in particular with regard to the influence of antipsychotic medication. Better insight into mechanisms of cannabis use might ultimately guide the development of effective treatment strategies.

CHAPTER 9 presents an editorial addressing the issue of differences in potency of cannabis (i.e. the amount of THC) in relation to its effects on psychosis and cognition. Apart from THC, cannabis contains a range of other cannabinoids, among others cannabidiol. Notably, cannabidiol has been shown to act anxiolytic and, as suggested by studies by Morgan and colleagues, might antagonize the negative effects of THC. This is of relevance as the composition of cannabis differs widely with regard to the ratio of cannabidiol and THC. It is concluded that future research on this topic is warranted in order to shed further light on the possibly antipsychotic mechanisms of action of cannabidiol. Furthermore the importance of considering differences in the cannabidiol:THC ratio of cannabis when studying its effects on human behavior and mental health is emphasized.

Finally, **CHAPTER 10** briefly summarizes the results of the studies presented in this thesis, which includes three epidemiological studies, an experimental neuroimaging, an observational study, two reviews and an editorial. The relevance of the current results is discussed on the background of existing findings. Furthermore, clinical implications are considered. Directions for future research are provided.