

# Investigating neurobiological mechanisms underlying comorbid cognitive symptoms in psychosis and substance use

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## Valorisation

The primary goal of scientific research in medicine is to I) increase knowledge II) to diminish illness and suffering thereby improving quality of life and III) in the future, prevention illness. To accomplish this goal, we need to develop new treatment strategies. The work described in this thesis was aimed at identifying possible molecular targets for development of new treatment strategies for cognitive symptoms of psychotic disorders and substance use disorders.

The first part of this dissertation was aimed at providing more insight into neurobiological mechanisms underlying the comorbid cognitive symptoms of psychosis. Psychotic disorders can be very disabling and may have a major negative influence on quality of life. The disorder is associated with a significant and long-lasting health, social, and financial burden, not only for patients but also for families, other caregivers, and the wider society. The costs of mental health care for psychotic patients worldwide are high. In The Netherlands the mental health costs for schizophrenia alone, the most severe form of psychotic disorders, are estimated at 517 million euros per year. Cognitive symptoms of psychosis are found to be predictive of functional outcome, relapse and medication compliance. Moreover, cognitive decline in adolescents with a psychotic disorder increases drop-out of school and is one of the main reasons why patients with psychosis struggle to find or keep jobs. Therefore, better treatment is urgently needed and being able to treat these symptoms could not only drastically improve quality of life of patients. It could also significantly reduce mental health costs as it leads to shorter admissions, more participation in society and less need for social support. The work presented in this dissertation was aimed at providing more insight into the neurobiological mechanisms underlying these symptoms and at identifying possible new molecular targets for development of cognitive enhancing pharmacological agents, since currently available antipsychotic medication mainly targets dopaminergic neurotransmission and have no or little beneficial effects on cognition. Therefore, it is highly important that the role of other neurotransmitter systems in the development of cognitive impairment are explored. We showed that the cholinergic system holds promise as a potential target for cognitive enhancement in psychosis which lays the groundwork for future studies. Our results also highlight the need for more personalized treatment rather than a protocol based approach given the highly heterogeneous (cognitive) profile observed in patients with a psychotic disorder. Although protocols and treatment guidelines are useful, the work described in this dissertation highlights the need

for extensive mapping of the individual profile and to accordingly adjust the treatment approach.

In the second part of this dissertation we tried to gain more insight into mechanisms underlying substance use disorders, thereby focusing on cannabis use. Cannabis is the most frequently recreational drug used worldwide. The lifetime prevalence of cannabis use among adolescents in the Netherlands is estimated at 23%. Approximately one out of 10 weekly cannabis users transitions to cannabis dependence. To date, the key question, why some people transit to cannabis dependence whereas others do not, remains unanswered. Another unanswered question is why people with psychotic disorders are more likely to use cannabis and to develop cannabis related disorders. The work included in this dissertation provides some insight into the mechanisms involved in continued, frequent cannabis use. We showed that cue-induced reactivity in the putamen, a brain region strongly involved in the formation of habits, predicted cannabis use related problems after a 3-year period. This suggests that habit formation is an important focus point for treatment of cannabis use disorders. Moreover, since this sensitized reaction to cannabis cues seems already present in early stages of cannabis use, this may be a valuable target in the prevention of cannabis use. Development of programs aimed at prevention of cannabis use disorders could also benefit from more insight in protective factors. The work included in this dissertation showed that studying patterns of substance use in patients with 22q11.2 deletion syndrome has the potential to provide insight in both genetic factors and protective environmental factors of substance use disorders given that these patients seem to have a decreased risk for developing substance use and substance use disorders. Additionally, because of the increased risk for psychotic disorders in this population, studying patterns of substance use and related disorders could also provide insight in the genetic aspect of substance use in schizophrenia.

Overall, the work reported in this dissertation is a small step towards a better understanding of the neurobiological mechanisms underlying comorbid cognitive symptoms in psychosis and substance use disorders in order to develop new and effective treatment and in the future, possibly preventive strategies of these disorders.