Translational research investigating psilocybin

Valorisation and Impact paragraph

In this section, the scientific and societal impact of the research presented in this dissertation is discussed.

Contribution to science

Psychedelics such as psilocybin have been around for centuries and were widely popular in the early 1960s. Various clinical and preclinical studies were conducted to explore the therapeutic potential of psilocybin to treat mental disorders, such as depression, anxiety, and addiction disorders. Unfortunately, psychedelic biomedical research was stagnated for decades due to social stigma and law restrictions in 1970. A renewed interest in psychedelic research has emerged and psychedelics have become widely popular for recreational, as well as therapeutic use in the last couple of years. In spite of the growing interest in psychedelics, there is still considerable debate regarding the underlying neurobiological mechanisms and its therapeutic potential.

In **chapter 2,** we gave a summary of the current available literature on the dose-dependent effects of psychedelics on the vertical (rodent vs human) and horizontal (healthy vs disease) aspects. We discussed the role of the acute subjective, mystical and hallucinogenic experience in the antidepressant effects of psychedelics. Ultimately, and most importantly, we identified the gaps in knowledge of translational psychedelic research and proposed a translational framework that could aid in future studies. We discussed that psychedelic research offers the possibility for a reverse translation of clinical human findings into preclinical models to investigate the underlying biological effects. In turn, the results of preclinical studies can be utilized to further optimize current psychedelic treatment therapies, for example by identifying molecular pathways responsible for both the antidepressant and adverse effects of these drugs. This information can contribute to developing novel molecules that exert psychedelic characteristics with an improved therapeutic window. We believe that such an approach has the potential of bringing advancements in the central nervous system (CNS) research field that has struggled to provide new solutions to long-existing problems. Currently, psychedelic research is dominated by clinical research, while preclinical research (in vivo, in vitro, in silico) is lacking greatly behind. **Chapter 2** stresses the importance of using a multi-disciplinary approach to investigate the therapeutic potential of psychedelics. We show the significance of utilizing rodent studies and the valuable information that can be collected through these studies. The translational framework that we proposed can be used as a guide for scientists in the psychedelic field. The model incorporates all scientific fields, from molecular to behavioral and clinical research. Only when all these aspects are addressed together, we may unravel the underlying neurobiological mechanism of psychedelics and understand their therapeutic potential. The

proposed translational model has been incorporated in this dissertation, thereby providing a mere example of how this model may be used in practice. This chapter also provides recommendations for future studies, which might be inspiring for other psychedelic researchers.

Chapters 3 and 4 contribute to preclinical psychedelic research. The aim of these two chapters was to investigate the acute dose-dependent effects of psilocybin on two cognitive domains, namely pattern separation and sensorimotor gating. Moreover, the microdialysis experiments in **chapter 3** demonstrated dose-dependent effects of psilocybin on the glutamate and GABA levels in the hippocampus and prefrontal cortex in rats. The results of this study give insights into the neurobiological mechanisms of psilocybin and demonstrate that at high psilocybin doses both the 5-HT_{2A} and 5-HT_{1A} receptors are stimulated, subsequently impairing cognition via the latter receptor. We discussed that lower doses of psilocybin might have potential pro-cognitive effects. This research can therefore be seen as a stepping-stone for future studies. Aside from underpinning the underlying neurobiological mechanism of psychedelics, this research, as well as that of **chapter 5**, enhanced the knowledge on the concept of pattern separation and sensorimotor gating itself and the contribution of the 5-HT_{2A} and 5-HT_{1A} to these cognitive processes.

Aside from investigating the molecular and behavioral effects of psilocybin in rodents, this dissertation also explores the effects of psilocybin in healthy volunteers. Taking into account the multi-disciplinary framework, various different scientific domains were investigated. For instance, the effect of psilocybin on cognition (flexibility), as well as physiological and epigenetic changes. In **chapter 7,** we aimed to investigate the underlying biological mechanisms of psilocybin by exploring the effect of a single medium dose of psilocybin on plasma circulating miRNAs (cimiRNA) in healthy volunteers. The results described in **chapter 7** are important for the scientific community because it indicates which miRNAs, targeted genes and pathways are associated with psilocybin's effect on the body and brain. We encourage the scientific community to further look into this, as it will aid to the understanding of the molecular effects of psilocybin in the brain eventually.

The review in **chapter 6** focuses on cimiRNAs and provides a comprehensive assessment on the potential value of cimiRNAs as CNS biomarkers for brain pathology. The review can be used as a reference database for scientists. Thus a miRNA of interest can be quickly found in the tables and information can be gathered such as (1) in which cognitive impairment diseases the miRNA is dysregulated, (2) whether the miRNA is up- or downregulated, (3) which analytical method has been used, (4) the group size of the clinical study, and (5) which bodily fluid has been used for cimiRNAs measurements. Several colleagues at Maastricht University are using this recent review as a database, and up-to-date the review has already been cited over 110 times (researchgate.net) indicating its value in the scientific community.

Contribution to society

The fundamental research that has been conducted in this dissertation not only aims to contribute to the scientific community but also aims to benefit society. In the next paragraphs, the societal impact and valorization of the research of this dissertation are discussed. Valorization is defined as: "The process of making knowledge gained from scientific education and research available or useful for economic or societal utilization, or translating it to competing products, services, processes and new entrepreneurship" (VSNU, 2013). Taking into account this definition, the clinical, as well as the economic impacts are delineated.

Chapters 2, 3, 4 and 7: Major depression disorder (MDD) is the most prevalent psychiatric disease and it has been estimated that worldwide more than 280 million people suffered from MDD in 2021 (Global Health data Exchange, 2021). Although there are many treatments for depression, this is not fully deployed in all patients. Only 50% of the patients respond to a first-line treatment, and one-third of the patients remain unresponsive to treatments (1, 2). This huge gap in adequate therapies has led clinicians to seek alternative methods such as psychedelics. Up to date, there are 11 active clinical trials that investigate the therapeutic potential of psychedelics, yet most studies only focus on the functional ability of psychedelics to modulate mood and anxiety, and only little preclinical research is performed into the molecular and underlying neurobiological mechanisms of psychedelics. In addition, only a handful of preclinical studies investigated the effects of psychedelics on cognition (i.e. pattern separation, cognitive flexibility, and sensorimotor gating). Understanding the positive, as well as the adverse effects of psilocybin is essential in the context of the therapeutic, as well as the recreational use of psilocybin. Information gathered from this dissertation can be used to understand the safety and effectiveness of psilocybin. Consequently, this research not only can have a clinical impact, but hopefully also facets the general debate about legalizing psychedelic drugs for therapeutic and recreational use.

Psychedelic research has strong clinical implications, yet the economic impact must not be overlooked. Currently, there are already 47 public psychedelic companies, 34 private companies, and 3 psychedelics exchange-traded funds (ETFs). Commercial companies seek to investigate existing as well develop new (non-hallucinogenic) psychedelic compounds with the goal to patent and market these. The potential revenues are expected to be very large. The alleged positive clinical effects of psychedelics have gained enormous media attention the last couple of years, which has actually initiated a hype to research psychedelics as well as invest in companies active in this specific area. Linked to this, this attention also generated more grant possibilities to research psychedelics in the academic field, thereby generating more staff and laboratories dedicated to investigate the effects of psilocybin and other psychedelics on neuronal integrity and its functional consequences.

Chapter 5: Schizophrenia is a highly prevalent occurring neuropsychiatric disorder, affecting approximately 1% of the population worldwide (3). Schizophrenia is a highly complex disorder, characterized by symptoms from three separate categories. Cognitive deficits are one of these three categories and are considered key features of schizophrenia, collectively known as cognitive impairment associated with schizophrenia (CIAS). Due to the heterogeneous nature of the disorder, finding a single effective treatment for each of the symptom categories is challenging. Cognitive performance is one of the best predictors of functional outcome in patients and therefore targeted treatment to enhance cognitive function in schizophrenia patients could greatly improve their quality of life. The results of chapter 5 demonstrate that targeting post-synaptic 5-HT_{1A} hetroreceptors might have beneficial effects on CIAS on multiple different domains (i.e. cognitive flexibility, pattern separation, and sensorimotor gating). Subsequently, the biased agonist F15599 shows therapeutic potential. A logical step from here onwards would be to investigate the effectiveness of F15599 in clinical trials with schizophrenia patients. If proven successful, patients would greatly benefit from this. Reducing CIAS symptoms in schizophrenia patients will furthermore reduce the social and economic burden of family and society as a whole, by reducing medical and caretaking costs. Lastly, the company Neurolixis, which owns the F15599 compound will also financially profit, as this will be the first drug on the market that specifically targets CIAS. If proven effective, biased agonists such as F15599 might also be a promising therapeutic strategy for other neuropsychiatric disorders. Consequently, this would help the companies active in this field to attract further financial resources for research and clinical trials and eventually market these compounds for different CNS disorders.

References

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