On the bumpy road of psychotic disorders

1. Impact paragraph

In this chapter, the impact paragraph, the (potential) impact of the research included in this dissertation on science and society will be addressed.

To develop mechanistically novel drugs and eventually provide personalized treatment approaches for psychosis and related disorders, we need a better understanding of the neurochemical systems in the brains of these patients. This dissertation contributed to this need by studying neurobiological processes in individuals with an increased risk of developing a psychotic disorder and individuals with non-affective psychotic disorders (NAPD).

1.1. Implications for science

In terms of scientific impact, this dissertation has several contributions to the existing literature. Our extensive literature review described in **chapter two** is the first to systematically combine neuroimaging studies that addressed the dopaminergic system of multiple high-risk groups for psychotic disorders. We found that striatal dopamine $D_{2/3}$ receptor availability is unaltered in clinical, genetic, and environmental high-risk individuals relative to healthy volunteers. In addition, we found that striatal dopamine synthesis capacity (DSC) was increased in people that meet clinical criteria for being at ultra-high risk of developing psychosis and individuals with 22q11.2 deletion syndrome (22q11DS), while striatal DSC was decreased in cannabis-using environmental high-risk individuals. These findings suggest that neuroimaging techniques might be useful to identify individuals who are likely to transition to NAPD.

In addition, we were one of the first to explore the availability of the striatal dopamine transporter in groups of subjects suffering from 22q11DS and 22q11.2 duplication syndrome (22q11DUP) (**chapter three**). The mean availability of the striatal dopamine transporter was numerically higher in individuals with 22q11DS than in healthy individuals, who had numerically higher availability of the striatal dopamine transporter than individuals with 22q11DUP. This is a contribution to the literature, as only a few molecular neuroimaging studies focused on individuals with 22q11DS and 22q11DUP and our findings confirm the presence of a hyperdopaminergic state in 22q11DS, which has been previously reported by others.[1-3] In addition, we identified the striatal dopamine transporter as a potential target to identify and prevent Parkinson's disease in individuals with 22q11DS.

With the exploratory study described in **chapter four**, we took steps to understand how various aspects of different neurotransmitter systems relate to each other in 22q11DS. These findings may encourage other scientists to investigate this in a larger sample. **Chapter four** also provided preliminary evidence that aspects of dopaminergic and cognitive functioning might be related to each other in 22q11DS.

This is a reason for future research to investigate the potential of dopaminergic drugs to reduce cognitive deficits in 22q11DS.

Our narrative review focusing on molecular aspects of nigral functioning in patients with schizophrenia (**chapter five**) is another add-on to the existing literature. Firstly, because the functioning of the substantia nigra in schizophrenia is relatively understudied relative to the striatum. Secondly, because we found evidence for hyperdopaminergic functioning, reduced γ-aminobutyric acid (GABA)-ergic inhibition, and excessive glutamatergic excitation in the substantia nigra of patients with schizophrenia. These results stimulate critical thinking about and might improve existing theoretical frameworks on the neurobiology of psychotic disorders. In addition, some of the alterations in nigral molecular functioning that we reported have the potential to be used as treatment targets or biomarkers in the future.

In **chapter six**, we combined, for the first time, neuromelanin-sensitive magnetic resonance imaging (NM-MRI) and [^{18}F]F-DOPA positron emission tomography in patients with NAPD and healthy individuals. We expected to find positive associations between these measures in both groups, but instead, we found a negative correlation in healthy individuals and no correlation in patients. From this, it is clear that additional work is needed to understand the meaning of the NM-MRI signal and before this potentially promising method can be used in clinical care to investigate the nigral aspects of the dopaminergic system in neuropsychiatric disorders.

In this dissertation, we also explored the associations between plasma concentrations of two prototypical endocannabinoids and different neurotransmitter systems in patients with NAPD and controls (**chapter seven**). This study is the first of its kind and combines multiple neuroimaging techniques. We found preliminary evidence that 2-arachidonoylglycerol (2-AG) is associated with frontal glutamatergic functioning in patients, but not in controls. It is also the first study worldwide to examine the relationship between striatal DSC and plasma levels of N-arachidonoylethanolamine (anandamide) and 2-AG in patients and controls. Although we found no statistically significant associations between these measures, we took a first step to understand why and how cannabis use might cause the development of psychotic disorders. Eventually, aspects of the endocannabinoid system might be used as drug targets.

Finally, besides investigating neurobiological processes, we also elaborated on the future perspective of moving towards a more personalized approach to treatments of psychotic and related disorders in mental health care (**chapter eight**). We did this by developing a machine learning model to identify clinical, familial, sociodemographic, and environmental variables that could potentially, in the future, predict treatment-resistance in patients with schizophrenia. The model utilized the unique data from the Genetic Risk and Outcome of Psychosis (GROUP) study[4] and showed modest

performance in predicting treatment-resistant schizophrenia. These findings provide future directions for the development of prediction models for psychotic and related disorders. For example, future research needs to investigate whether the model's performance can be improved by adding data from different modalities, as well as, whether prediction models are usable and useful in clinical practice. Essential next steps are also the improvement of the external validation of prediction models and the implementation of these models in real-world settings. Preferably, clinicians should be involved in the development of these practical tools to guide treatment choices in order to bridge the gap between research and clinical practice.

So far, the research included in this dissertation has been well-received in the international academic world. Most results have been published or are currently under review in a peer-reviewed scientific journal, and hence accessible to psychiatric care providers and researchers. Some of the research is published in Open Access journals. Additionally, I have disseminated some of the findings at international scientific conferences (i.e., the Schizophrenia International Research Society conference, the European College of Neuropsychopharmacology [ECNP] conference, and the ECNP neuropsychopharmacology workshop for early career scientists).

1.2. Implications for society

In terms of societal impact, there is still a long way to go. However, I hope that this dissertation will contribute to the development of a more differentiated approach to pharmacological treatments for psychosis and related disorders and eventually the adjustment of treatment guidelines. Moreover, I hope that this dissertation will contribute to the accurate prediction of transition risk to NAPD in high-risk individuals, as well as, treatment response in patients with NAPD. Adjusting the current treatment guidelines and providing personalized treatment options to patients have the following potential long-term impact.

First, it might greatly improve the quality of life of many patients with psychotic or related disorders. During my PhD research, I came in contact with young adults with NADP, 22q11DS, and 22q11DUP. It was devastating to see how, in some cases, their lives were halted due to the symptoms they experienced. This often meant that they could not go to school or work, were isolated from friends and family, and that they could not take care of themselves. In addition, for some of them, it was difficult to find effective medication, which had a judge impact on their quality of life. In general, ineffective treatments result in the discouragement of patients, extended treatment trajectories, chronicity, and high societal costs. Therefore, providing patients with effective treatment sooner might improve these negative consequences and might also be beneficial for the long waiting times for psychiatric care, the high workload for psychiatric care providers, and increase the cost-effectiveness of treatments.

Additionally, on multiple occasions, patients seemed unpleased with the treatment choices that were made by the clinicians. The use of practical tools to guide treatment choices might, therefore, help to improve shared decision-making in the future. For instance, the outcome of these tools might be explained to the patient by the clinician, which facilitates the involvement of patients in this process. This will also make it more understandable for patients why certain treatments are likely to be useful for them, which will make it more appealing to engage in treatment.

As the results of this dissertation may contribute to the future development of personalized treatment approaches for psychotic and related disorders, our findings might not only be relevant to patients but also to psychiatric care providers, health insurance companies, and policymakers. Moreover, our findings might also be relevant to drug companies. Recently, some companies have been involved in the development of agonists for the serotonin 2A receptor.[5] However, more drug companies need to invest in psychiatry, possibly through the engagement of charitable funders and the government. The findings of this dissertation emphasize the importance of such initiatives/collaborations.

Besides working as a researcher, I have also been working as a science editor since the last year of my PhD. In this way, I attempt to communicate research findings to people outside of academia. Some findings of this dissertation have also been presented at local science events organized at a mental health care centre.

In conclusion, the research included in this dissertation is a small, but important step towards a better understanding of neurobiological processes in patients with psychotic and related disorders. This knowledge is needed to develop novel selective drugs, as well as, a more differentiated approach to pharmacological treatments for psychosis and related disorders. Additionally, this knowledge might be useful to accurately predict transition risk to NAPD in high-risk individuals, as well as, the response to antipsychotic treatment in patients with NAPD in the future. Possibly, this will then contribute to the development of personalized prevention and intervention approaches for psychotic and related disorders.

References

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