On the bumpy road of psychotic disorders

Chapter

Summary

1. Summary of main findings

The overall aim of this dissertation was to advance the current knowledge on neurobiological processes in individuals with an increased risk of developing a psychotic disorder and individuals with non-affective psychotic disorders (NAPD) by using several imaging approaches. By doing so, this work may contribute to the development of a more personalized approach to treatments for psychotic disorders in mental health care. In the first part of this dissertation, neurobiological mechanisms were examined in individuals at increased risk of developing a psychotic disorder, in particular those with 22q11.2 deletion syndrome (22q11DS) (**chapter two – chapter four**). In the second part of this dissertation, neurobiological mechanisms were examined in individuals with NAPD (**chapter five – chapter seven**). To implement personalized treatment approaches in psychosis care, clinicians might use prediction models in the future. These models could utilize, for example, neuroimaging, clinical, and/or sociodemographic data, and support clinical decision-making. In the third part of this dissertation, we elaborate on this future perspective (**chapter eight**). In this chapter, the key findings of this dissertation are summarized.

1.1. Neurobiology of individuals with an increased risk of developing a psychotic disorder: 22q11DS

For more than fifty years, schizophrenia research has mainly been focused on dopaminergic abnormalities.[1] Therefore, in **chapter two**, neuroimaging studies that address several components of the dopaminergic system in individuals at increased risk of developing a psychotic disorder were reviewed. We divided the study cohorts of the reviewed studies into three groups: individuals with a clinical, genetic, or environmental high risk of developing psychosis. The current evidence highlights that striatal dopamine $D_{2/3}$ receptor availability is unaltered in all three high-risk groups compared with healthy individuals. In addition, we found that striatal dopamine synthesis capacity (DSC) was increased in some clinical and genetic high-risk individuals relative to controls (e.g., people that meet clinical criteria for being at ultra-high risk [UHR] of developing psychosis and individuals with 22q11DS), while striatal DSC was decreased in cannabis-using environmental high-risk individuals. It seems therefore likely that individuals with an increased risk of developing psychosis can be stratified into multiple subgroups, with varying risks to develop psychosis and underlying neurobiology. Overall, these findings support the hypothesis that dopaminergic abnormalities already occur in some high-risk individuals before they develop a psychotic disorder. These alterations may facilitate early detection and intervention of psychotic disorders.

As adults with 22q11DS also have an increased risk of early-onset Parkinson's disease[2] and this disease is characterized by the loss of striatal dopamine transporter binding,[3] we aimed to investigate differences in the availability of the striatal dopamine transporter between individuals with 22q11DS, individuals with 22q11.2 duplication

syndrome (22q11DUP), and healthy volunteers in **chapter three**. For this purpose, we set up an [^{123}I]FP-CIT single photon emission computed tomography (SPECT) study in individuals with 22q11DS or 22q11DUP and healthy volunteers. Although we found no statistically significant group differences, individuals with 22q11DS had numerically higher mean striatal [^{123}I]FP-CIT binding ratios than HC, who had numerically higher mean striatal [^{123}I]FP-CIT binding ratios than individuals with 22q11DUP. As we did report some moderate-to-large effect sizes, this suggests that group differences could be verified in a somewhat larger cohort. Future larger studies are necessary to replicate our preliminary findings and investigate whether dopamine transporter imaging could be used as a predictor of progression to Parkinson's disease in individuals with 22q11DS.

Besides investigating whether neurochemical changes occur in the brains of individuals with an increased risk of developing a psychotic disorder, it provides additional insight to know how these neurochemical changes relate to clinical symptomatology in these patients, as well as, how changes in several neurotransmitter systems interrelate. Therefore, in **chapter four**, we explored, using proton magnetic resonance spectroscopy (^{1}H-MRS) and [^{18}F]fallypride positron emission tomography (PET), the relationships between 1) dopamine $D_{2/3}$ receptor availability in the striatum and anterior cingulate cortex (ACC) and 2) glutamate, glutamine, and their combined (Glx) concentrations in the striatum and ACC of individuals with 22q11DS. Additionally, we examined the role of striatal and frontal dopamine $D_{2/3}$ receptor availability in cognitive functioning in 22q11DS, as well as, the association between ACC brain volumes and the concentration of glutamate, glutamine, and Glx in the striatum and ACC of 22q11DS and healthy volunteers. Even though we found no significant associations between frontal or striatal dopamine $D_{2/3}$ receptor availability and glutamate or related metabolite concentrations, our effect sizes were comparable to findings in patients with psychosis. As our sample size was limited, we can therefore not rule out that an association between dopaminergic and glutamatergic functioning does exist in 22q11DS. Moreover, before Bonferroni correction for multiple testing, we found associations in healthy controls between right rostral ACC volume and glutamate concentration in the ACC, between left caudal ACC volume and glutamine concentration in the ACC, and between right caudal ACC volume and Glx concentration in the ACC. No such associations were found in 22q11DS, which suggests that the associations between ACC volumes and glutamate, glutamine, and Glx concentrations in the ACC might differ between groups. Lastly, within the 22q11DS group, the association between dopamine $D_{2/3}$ receptor availability in the left ventral striatum and verbal memory, as well as, the associations between dopamine $D_{2/3}$ receptor availability in the ACC and visual memory, executive functioning, and the composite cognitive score, reached statistical significance. The effect sizes were

noteworthy (i.e., corresponding to strong effects). This suggests that a relationship between dopamine $D_{2/3}$ receptor availability and cognitive functioning might be verified in a larger sample. Although our exploratory study did not reveal a statistically significant association between dopaminergic, glutamatergic, and cognitive functioning, the effect sizes warrant future research on this topic.

1.2. Neurobiology of individuals with a non-affective psychotic disorder

Despite being one of the main origins of dopaminergic input to the striatum, the substantia nigra has been relatively understudied in schizophrenia, in comparison to other brain regions. Hence, in **chapter five**, we presented a literature overview of post-mortem and molecular imaging studies that addressed molecular alterations in the substantia nigra of patients with schizophrenia. We found evidence for hyperdopaminergic functioning in the substantia nigra of patients with schizophrenia (i.e., increased aromatic L-amino acid decarboxylase activity in antipsychotic-free/-naïve patients and elevated neuromelanin accumulation). Reduced γ-aminobutyric acid (GABA)-ergic inhibition (i.e., decreased density of GABAergic synapses, lower vesicular GABA transporter messenger ribonucleic acid [mRNA] levels and lower mRNA levels for $GABA_A$ receptor subunits), excessive glutamatergic excitation (i.e., increased NR1 and Glur5 mRNA levels and a reduced number of astrocytes), and several other disturbances implicating the substantia nigra (i.e., alterations in immune functioning and copper concentrations) could potentially underlie this nigral hyperactivity and associated striatal hyperdopaminergic functioning in schizophrenia. These results highlight the importance of the substantia nigra in the pathology of schizophrenia and suggest that some aspects of molecular functioning in the substantia nigra could potentially be used as treatment targets or biomarkers.

As shown in this dissertation, the dopaminergic system is often investigated *in vivo* by the use of SPECT and PET imaging, such as [^{18}F]F-DOPA PET. However, as these techniques involve exposure to ionizing radiation (which frightens many patients) and can be time-consuming and expensive, we would preferably make use of an alternative method to assess the dopaminergic system, such as neuromelanin-sensitive magnetic resonance imaging (NM-MRI). Before alternative methods can be used in clinical practice, the interrelationships between NM-MRI and PET/SPECT measures should be investigated. Accordingly, in **chapter six**, using NM-MRI and [^{18}F]F-DOPA PET, we investigated the relationship between striatal DSC and neuromelanin in the substantia nigra of patients with NAPD and healthy volunteers. For this purpose, we set up an NM-MRI and [^{18}F]F-DOPA PET study in patients with NAPD and healthy volunteers. In healthy volunteers, we found subsets of voxels within the substantia nigra where NM-MRI signal correlated negatively with DSC in the whole striatum and DSC in the limbic striatum. This was not the case for patients. The negative correlation in

healthy volunteers might be explained by vesicular monoamine transporter-2 (VMAT-2) functioning, while a lack of a correlation in patients might be due to the small sample size, effects of symptom severity or antipsychotic medication. In addition, these findings indicate that [^{18}F]F-DOPA PET and NM-MRI are measures that reflect different aspects of dopaminergic functioning. Striatal [^{18}F]F-DOPA PET might reflect a dynamic, state-like, aspect of dopaminergic functioning, while NM-MRI signal in the substantia nigra might reflect a chronic, trait-like, aspect of dopaminergic functioning. Future studies should assess the interrelationships between DSC, neuromelanin, VMAT-2, and related processes in larger homogeneous cohorts. As NM-MRI is more accessible than PET imaging, this might eventually enable clinicians and researchers to study specific aspects of the dopaminergic system in humans more efficiently and at lower costs. Further research into the exact meaning of the NM-MRI signal is, however, first needed.

Besides neuroimaging markers, other more easily obtainable markers (e.g., blood markers) might be useful to stratify NAPD patients into subgroups. Hence, in **chapter seven**, we assessed differences in plasma concentrations of endocannabinoids between NAPD patients and healthy individuals. Plasma concentrations of N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) were determined by use of liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). Contrary to expectation, the plasma concentration of anandamide was significantly lower in patients than in healthy individuals. This did not change after corrections for sex and lifetime cannabis use, and might be explained by the usage of antipsychotic medication that could downregulate anandamide concentrations in blood. We found no group differences with regard to 2-AG plasma concentrations. Additionally, we investigated whether endocannabinoid plasma concentrations were related to dopaminergic, glutamatergic, and GABAergic functioning in both groups, as assessed with [^{18}F]F-DOPA PET and ^{1}H-MRS. We demonstrated a negative association between 2-AG plasma concentration and frontal Glx concentration in patients and a non-significant positive association in healthy individuals. The interaction between group and 2-AG plasma concentration was significantly associated with frontal Glx concentration. Plasma concentrations of 2-AG did not seem to be related to frontal GABA concentrations or striatal DSC in patients or healthy individuals. We also found no compelling evidence for relationships between anandamide plasma concentrations and measures of dopaminergic, glutamatergic, and GABAergic functioning in either group. These preliminary results suggest that peripheral 2-AG might modulate frontal glutamatergic functioning differently in patients with NAPD than in controls. We reported no evidence of a mediating role for peripheral anandamide in regulating neurotransmission. More research in larger cohorts is needed to replicate our findings.

1.3. Towards an individualized approach of disease: Precision psychiatry

Eventually, the obtained information about neurochemical systems in the brains of individuals with an increased risk of developing a psychotic disorder and patients with NAPD might contribute to improved treatment approaches. In addition, the outcome of prediction models, that utilize information about neurochemical processes, might be used as an early indicator of neuropsychiatric disorders or guide treatment choices. Due to the complexity of NAPD, additional information, such as data about clinical and sociodemographic variables, might be necessary to allow for the stratification of patients into subgroups. Therefore, in **chapter eight**, by use of a machine learning model and data from the Genetic Risk and Outcome of Psychosis (GROUP) study, we assessed whether clinical, familial, environmental, and sociodemographic variables, which could potentially predict treatment-resistant schizophrenia (TRS) in the future, were associated with TRS in patients with NAPD. We selected patients who met TRS or antipsychotic-responsive criteria throughout the GROUP study period. The machine learning-based analysis consistently revealed that poor premorbid functioning and younger age at illness onset were important variables that could predict TRS in these patients. In the sensitivity analysis, for which we only selected patients who met the TRS or antipsychotic-responsive criteria at a follow-up assessment but not at the baseline assessment of the GROUP study, we found that poor premorbid functioning and lower educational level were important for the prediction of TRS. Although our machine learning models based on clinical, sociodemographic, familial, and environmental variables only showed a moderate performance in predicting TRS, our findings provide an important base on which precision medicine for TRS can be improved. Future large multi-centre studies are needed to investigate whether the model's performance can be enhanced by adding data from several modalities.

2. References

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