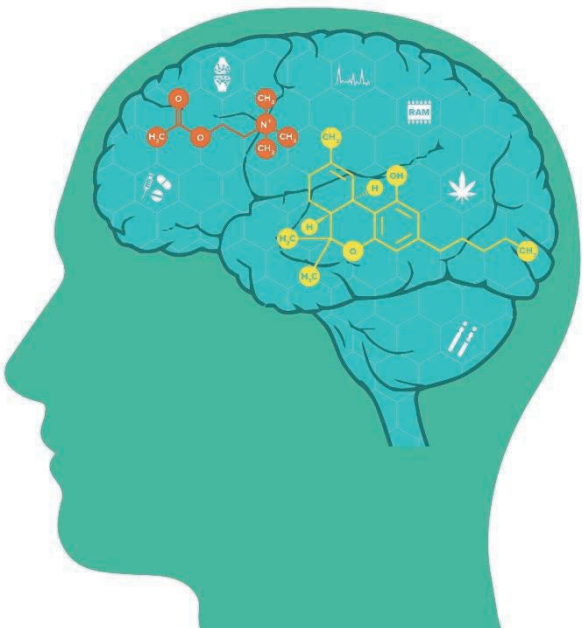
Investigating neurobiological mechanisms underlying comorbid cognitive symptoms in psychosis and substance use

Chapter | 8

Summary and general discussion



Summary

The overall aim of this thesis was to provide more insight into the neurobiological mechanisms underlying comorbid cognitive symptoms in psychosis and continued frequent substance use. In the first part of this thesis, neurobiological mechanisms of cognitive symptoms in subjects with a psychotic disorder were examined (chapter 2 – chapter 4), with a focus on the cholinergic system. In the second part of this thesis, underlying neurobiological mechanisms of substance use were examined, focusing on mechanisms underlying continued frequent cannabis use (chapter 5 – chapter 7). In this final chapter, the main findings of these studies are summarized and discussed as well as the clinical implications of these findings and future directions.

In **chapter 2**, the effectiveness of pharmacological interventions for separate cognitive domains critically impaired in schizophrenia patients, as established by the MATRICS initiative, were reviewed. The reviewed studies provided evidence for a role of the dopaminergic D_1 receptor subtype in processing speed and reasoning and problem solving. The serotonergic, GABA-ergic and glutamatergic system were found to be involved in different aspects of memory. The latter system was also found to be involved in reasoning and problem solving. Finally, nicotine acetylcholine receptors (nAChRs) have been found to modulate attention and vigilance. However, results from a limited number of studies suggested that memory functions may be enhanced with agents targeting the muscarinic system. Overall, these findings indicate that different mechanisms underlie separate aspects of cognition which suggest that patients with schizophrenia with different cognitive profiles may benefit from different intervention strategies.

In **chapter 3**, the role of the muscarinic M_1 receptor in cognitive function in subjects with a psychotic disorder was examined by means of the M_1 antagonist biperiden as a pharmacological challenge. Blocking the M_1 receptor significantly impaired both visual and verbal learning and memory which is indicative of a role of this receptor in these cognitive domains. An interaction effect was found between medication and group on reasoning and problem solving; in the psychosis group this domain improved after biperiden administration, whereas performance on this domain in the healthy control group worsened after biperiden administration. This indicates that the effect of M_1 antagonism on this domain was different for both groups. The effects of biperiden on the other cognitive domains were comparable in the psychosis and the healthy control group. Although these

results confirm a role of the M_1 receptor subtype in memory performance, the lack of a differential effect of M_1 blockade between the studied groups could indicate that M_1 receptor deficits were not present in our sample and are possibly only present in older, chronic schizophrenia patients.

Chapter 4 elucidates on the role of the cholinergic system in psychosis and associated cognitive impairments. We examined whether brain choline (cho) concentrations in the anterior cingulate cortex (ACC) and striatum differed between subjects with a psychotic disorder and controls and whether blockade of the M_1 receptor influenced cho concentrations in these regions. In addition, it was examined if cho concentrations were associated with separate domains of cognition. The significant inverse correlation between attention and striatal cho found in the psychotic subjects confirms previous findings of a role of the cholinergic system in cognitive symptoms of psychosis. Although we cannot rule out that there are cholinergic abnormalities present in chronic schizophrenia patients, the lack of a significant difference in cho concentrations between the groups, both after biperiden and placebo, in both brain regions could indicate that no severe cholinergic abnormalities were present in this sample of relative young and well-functioning psychotic subjects.

In **chapter 5,** the relationship between working memory network function and continued, frequent cannabis use was examined in a longitudinal 3-year follow-up functional MRI study. In the baseline study, it was found that despite comparable working memory network functioning and performance on a working-memory task (behavioral) in heavy cannabis users and healthy non-using control subjects, a stronger working memory network response was related to increased weekly cannabis use over a 6-month period. The follow-up results showed that despite improved performance on the working memory task in both groups, working memory network function did not change over the 3-year period. Contrary to previous findings, no association was found between baseline working memory network response and cannabis, nicotine, alcohol or other recreational drug use. These results suggest that continued cannabis use does not significantly influence working memory network functioning.

Elaborating on previously findings of increased activation in response to cannabis cues in heavy cannabis users compared to controls in the ventral tegmental area (VTA), as well as a higher activation in the ACC, orbitofrontal cortex (OFC) and striatum in more problematic cannabis users compared to less problematic

cannabis users, **chapter 6** describes the results of a follow-up study investigating the value of neural cue-reactivity in these brain regions in predicting changes in weekly cannabis use and related problem severity over a 3-year period. None of the regions identified in the baseline study were found to predict weekly cannabis use at 3-year follow-up. However, increased activation in the left (dorsal) striatum predicted cannabis related problem severity after 3 years which suggest cue-reactivity might be a useful tool in predicting transition to problematic cannabis use and possibly cannabis dependence.

In **chapter 7,** the prevalence of substance use and substance use disorders in 22q11.2 deletion syndrome (22q11DS), a population at high risk for developing psychotic disorders, was determined. The deletion on chromosome 22q11.2 defining this group of patients includes genes which have been associated with both psychotic disorders and substance use disorders. Therefore, investigating patterns of substance use in these patients may provide valuable insight in the genetic aspects of both psychosis and substance use disorders. Compared to psychotic patients (88%) and healthy controls subjects (82%), the prevalence of overall substance use (37%) and substance use disorders (1.2%) was low in 22q11DS patients. Furthermore, we found that these patients were at *decreased* risk for overall substance use as well alcohol and nicotine use separately. Interestingly, prevalence of recreational drug use did not differ between the three groups. In addition, within the 22q11DS group no relationship was found between prevalence of substance disorders and psychosis, COMT-genotype and intelligence quotient (IQ). Comparable to findings in the general population, substance use was more common in male than in female 22q11DS patients. Further research into both neurobiological and environmental factors contributing to this decreased risk of substance use and substance use disorders in 22q11DS could provide new insights in the genetic aspects of substance use disorders in both psychotic patients as well as the general population.

General discussion

The overall aim of this dissertation was to further examine neurobiological mechanisms underlying cognitive functioning in subjects with a psychotic disorder and substance use, heavy cannabis use in particular. In the first part of this dissertation, previous conducted studies investigating the effects of several pharmacological treatment strategies on cognitive symptoms in psychosis were reviewed. Furthermore, the role of the cholinergic system in these symptoms was examined. In the second part, possible neurobiological mechanisms of continued, frequent cannabis use were investigated using a longitudinal design. Moreover, prevalence and patterns of overall substance use and substance use disorders in 22q11.2 deletion syndrome (22q11DS) were examined in order to provide insight in genetic aspects contributing to substance use disorders.

Neurobiological mechanisms underlying cognitive symptoms of psychosis

Identifying potential targets for cognitive enhancement in schizophrenia: evidence from previous studies

The urgent need for effective treatment strategies for cognitive impairments reported by patients with a psychotic disorder has led to a tremendous increase of studies attempting to identify molecular targets which can enhance cognition in these patients. In **chapter 2**, several of these studies were reviewed. Both studies examining the effects of existing antipsychotics, which mainly target the dopaminergic D_2 and serotonin 2A ($5\text{-}HT_{2A}$) receptors, as well as studies examining pharmacological interventions targeting other systems were taken into account. An important observation is that the studies reviewed in this chapter do not provide evidence for positive effects of neither atypical and typical antipsychotics on cognitive impairments in schizophrenia, despite previous suggestions that atypical antipsychotics are superior to first-generation antipsychotics in treatment of cognitive symptoms (1). Although overall results have been unsatisfactory, some potential molecular targets have been identified over the years. Among the targets that hold promise for enhancement of cognitive function in psychosis are the dopamine D_1 receptors, serotonin $5\text{-}HT_{1A}$ and $5\text{-}HT_{3A}$ receptors, nicotinic α_7 receptors, $GABA_A$ receptors and NMDA receptors. It appears that dysfunction in separate cognitive domains are related to different neurobiological processes which could partly explain unsatisfactory results as the majority of the studies combine separate cognitive domains in one overall cognitive composite score.

Neurobiological mechanisms underlying cognitive impairment in psychosis: role of the cholinergic system

Although the cholinergic system has been repeatedly linked to a variety of cognitive domains (2), relatively little in-vivo research has been conducted on the role of cholinergic neurotransmission in psychotic disorders (3). Nonetheless, abnormalities in both nicotine acetylcholine receptors (nAChRs) and muscarinic acetylcholine receptors (mAChRs) have been described in post-mortem brains of patients with schizophrenia (4–10). However, due to the design of these post-mortem studies, it is currently unknown how these cholinergic abnormalities relate to cognitive impairments in these patients. Therefore, the aim of **chapters 3** and **4** was to provide more insight in this relationship in-vivo. We focused on the muscarinic M_1 receptor subtype because this subtype has been linked to both psychosis and cognition and because of all the mAChR subtypes, it has the highest expression rates in the central nervous system (CNS), particularly in brain regions instrumental for cognitive function including the striatum, frontal cortex and the hippocampus. We differentiated between 7 cognitive domains which have been found to be critically impaired in schizophrenia as established by the Measurement and Treatment to Improve Cognition in Schizophrenia (MATRICS) initiative since our findings in **chapter 2** indicated that separate domains of cognition are associated with different neurobiological mechanisms. Cognitive functioning was measured with the Cambridge Neuropsychological Automated Test Battery (CANTAB) schizophrenia test battery which covers all the MATRICS domains and is considered to be the 'golden standard'. In line with previous studies in both animals and humans, the findings described in **chapter 3** provide evidence for a role of the M_1 receptor in (verbal and visual) memory. Contrary to previous findings, acute M_1 receptor blockade did not affect working memory in both psychotic subjects and healthy controls, which could be related to characteristics of the task we used. Moreover, the lack of a differential effect between the two groups suggests that, contrary to post-mortem findings in schizophrenia (6,7,11), M_1 deficits were not present in our sample. However, it must be noted that M_1 receptor density has been found to decrease with increasing age in healthy subjects (12) and that our participants were younger than the patients included in previous post-mortem studies. Nevertheless, these findings are in line with the lack of difference in choline concentrations in the ACC and striatum between medication-free subjects with a psychotic disorder and healthy controls (after placebo) described in **chapter 4**. These latter findings are in contrast with previous studies reporting increased choline concentrations in both first-episode and chronic and medicated and un-medicated psychotic patients in different brain

regions (13–15). Compared to these studies however, our sample was smaller and we included subjects with a diagnosis within the psychosis spectrum instead of limiting the inclusion criteria to schizophrenia. This, in addition to the positive relationship found between choline concentrations and duration of untreated psychosis (16), could suggest that cholinergic abnormalities are only present in older patients with (chronic) schizophrenia or in a subgroup of patients with severe cognitive impairments as proposed by Scarr and colleagues (11). The psychotic subjects we included displayed less severe cognitive impairments compared to schizophrenia patients generally included (17). Although this hypothesis has not been investigated, our finding of an inverse correlation between striatal choline levels and attention in psychotic subjects but not in controls (**chapter 4**), would be in line with this hypothesis since attention was one of the few cognitive domains on which subjects with a psychotic disorder performed significantly worse than healthy controls. The lack of effect of M_1 blockade on attention and vigilance in **chapter 3** suggests that this cognitive domain may be primarily modulated by the nAChRs or other mAChR subtypes. This would be in line with previous studies (**chapter 2**) describing a positive effect of nicotine in healthy smoking and non-smoking individuals (18) and nicotine and nicotinic α_7 receptor agonists on attention in schizophrenia (19,20). Moreover, non-selective mAChR antagonists such as scopolamine have been found to impair attention, besides memory (21). To summarize, these findings confirm a role for the muscarinic cholinergic, and possibly nicotinergic system in cognitive functioning in subjects with a psychotic disorder, warranting further research. To investigate our hypothesis of more prominent cholinergic abnormalities in chronic patients, future studies should include both psychosis patients in the early phase and in a later stage of the disease. Alternatively, a longitudinal design could be used to examine progressive cholinergic abnormalities in psychosis. Moreover, future studies using a similar paradigm should use multiple day treatment with biperiden to examine delayed effects on cognition. Preferably, future research includes a direct in-vivo measurement of M_1 receptor expression using for example ^{123}I-IDEX single photon emission computed tomography (SPECT) imaging in both patients and healthy controls (22).

Neurobiological mechanisms underlying substance use disorders and continued, frequent cannabis use

The second part of this dissertation was aimed at identifying neurobiological processes involved in substance use and substance use disorders, focusing on mechanisms cannabis use. In **chapters 5** and **6** we tested the (predictive) relation

between working memory network function (as a part of regulatory executive functions and cognitive control) and cue-reactivity (as a part of motivational processes) and continued, frequent cannabis use over a 3-year period. Both processes could provide new insights in the development of substance use disorders since they are considered features of two core aspects underlying addiction: imbalanced regulatory functions and motivational processes (23–26). In **chapter 5**, we found that working memory task performance was comparable between heavy cannabis users and healthy controls and increased in both groups after 3 years. However, working memory network function did not differ between the two studied groups and did not change over the 3-year period, implying that cannabis does not have negative effects on working memory network function. This would in turn suggest that the effects on working memory performance and function may be substance specific since impaired working memory has been found in heroin and cocaine users (27–29). Furthermore, the lack of impaired working memory in gambling addicts (27) could indicate that impaired working memory is the result of the use of specific substances of abuse instead of it playing a causal role in the overall development of substance use disorders. These hypotheses could be investigated in future longitudinal studies. By means of regular monitoring of working memory network function in a large cohort of non-using, recreational using and heavy substance using adolescents, more insight can be provided in the causal role of working memory network functioning in development of substance use disorders. By comparing groups of different substance users, substance specific negative effects on working memory can be examined.

Interestingly, although in the baseline study working memory network functioning was found to predict cannabis use after 6 months, such a predictive relation was not found after 3 years. These contradictory findings could be due to loss of power since 7 heavy cannabis users dropped out at follow-up. Therefore, replication in a bigger sample is warranted. However, these findings could also indicate that predictors of short-term cannabis use differ from those predicting long-term use. Alternatively, given the predictive relation between cannabis cue-induced activity in the dorsal striatum and problem severity we found in **chapter 6**, this could indicate that regulatory executive control processes and motivational processes have differential roles in recreational cannabis use and problematic use, since motivational processes are considered to be expressions of sensitized and conditioned responses towards substance related cues (26). Since neural cue-reactivity did not predict the amount of cannabis use at follow-up, this suggests that cannabis-induced activity in the dorsal striatum could be a predictor of

cannabis addiction. Unfortunately, cannabis dependence was not assessed at baseline, causing this hypothesis to remain speculative. Contrary to the differential effects of different substances on working memory, striatal cue-reactivity is less likely to be substance specific since comparable results have been found in heavy alcohol users and addiction (30–32). Motivational processes are mediated by the reinforcing properties of substances because of the ability to strengthen the conditioned response (33). During transition from recreational (reward driven drug use) to addiction, a shift occurs from positive reinforcing effects of substances and impulsive behavior, mediated by the ventral striatum and the medial prefrontal cortex, to automatic, compulsive drug use and negative reinforcement (withdrawal) which has been linked to the dorsal striatum and lateral prefrontal cortex (25,34).

The results described in **chapter 7** suggest that genetic factors may contribute to the rewarding properties of substance of abuse and thus mediate motivational processes including cue-reactivity. In this chapter we found a low prevalence and decreased risk of substance use and substance use disorders in patients with 22q11.2 deletion syndrome (22q11DS), a genetic disorder characterized by a deletion on chromosome 22. We hypothesized that this lower risk of substance use and substance use disorders may be related to different reward processing in these patients. fMRI studies have found a decreased striatal BOLD response in subjects with substance use disorders during non-drug related reward anticipation (35,36) and increased brain activation during drug reward anticipation (37). Although little research has been conducted on reward processing in 22q11DS, one study reports no difference in striatal activity during monetary reward anticipation and decreased activation in medial frontal areas in these patients (38), which could indicate a decreased hedonic response. A decreased hedonic response could in turn be related to the decreased risk of substance use in these patients. These potential reduced rewarding effects of substances in 22q11DS could be related to dopaminergic abnormalities as a result of reduced COMT activity in these patients (39). Processing of reward is primarily modulated by dopaminergic neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens, which is part of the ventral striatum, and frontal cortex (40). The dopaminergic system as well as the striatum and frontal cortex are strongly involved in both psychotic and substance use disorders. Interestingly, despite the high risk of developing a psychotic disorder in 22q11DS, we did not find a relation between psychosis and substance use in these patients despite increased substance use and substance use disorders in schizophrenia. Studying the relation between altered neurobiological mechanisms due to 22q11DS and patterns of

substance use could provide more insight in the role of specific genes in the development of substance use disorders in both psychotic and healthy populations. Future genetic studies should therefore focus on genes lying within the deleted region of 22q11DS. Furthermore, studying the role of dopaminergic abnormalities (related to genetic variation) in reward processing in 22q11DS, psychosis and substance use disorders using a similar paradigm could provide further insight in the role of motivational processes underlying substance use disorders.

To summarize, regulatory executive functions and motivational processes may have differential roles in the transition from recreational substance use to substance use disorders.

Methodological considerations

The results described and discussed in this dissertation should be considered in the context of several methodological strengths, limitations and differences between studies. Although strengths and limitations are described in the separate chapters, a few overall strengths and limitations as well as differences in methods are mentioned here because they are important for the entire research field.

Contrary to the majority of previous conducted studies, an important strength of the studies described in **chapters 3** and **4** are the inclusion of medication-free subjects with a psychotic disorder as this eliminates acute confounding effects of antipsychotics. Furthermore, we conducted an extensive and well validated cognitive test battery (CANTAB) which is considered to be the 'gold standard' in psychosis research, enabling us to differentiate between the separate cognitive domains critically impaired in schizophrenia as established by the MATRICS. An important strength of the studies described in **chapters 5** and **6** is the use of a longitudinal design. These studies are the first studies that used a 3-year follow-up measurement enabling examining consequences of long-term use cannabis.

The unsatisfactory results of the studies that were reviewed in **chapter 2** could be at least partly related to methodological shortcomings of several of the reviewed studies. For example, in pharmacological intervention studies, the agent of interest is often prescribed as add-on therapy besides antipsychotic medication which may interact with the added agent since the exact mechanism of actions of antipsychotics are often not known (41). Moreover, these mechanisms of action differ across the different types of antipsychotic drugs, which is often not controlled for. An additional problem when studying neurobiological mechanisms in psychosis is excessive substance use in a substantial number of patients since substances of abuse, including alcohol, nicotine and cannabis influence the results.

Moreover, methodological differences between studies make it difficult to compare results of these studies. For example, use of different cognitive tests and different doses of medication could contribute to the inconsistent findings across studies. To minimize these methodological differences, the MATRICS initiative has been established, and since then a shift to standardized test batteries is observable.

When comparing our findings described in **chapter 4** to other studies, it is noticeable that the results vary greatly between studies. These inconsistent findings are probably related to differences in data acquisition and analyzing methods. Perhaps the most important difference between studies is the strength of the magnetic field (expressed in Tesla) used. Since the different resonance signals are determined by the strength of the external magnetic field (42), higher field strength leads to more specific, reliable results. Higher field strength increases the signal to noise ratio (SNR) and narrows the width of the peak resulting in better spectral resolution and sensitivity (42). Other important factors contributing to the reliability of MRS data are the size and location of the brain region measured (42). Because of differences in magnetic susceptibility between tissue types, it is difficult to acquire spectra of good quality in brain regions adjacent to other types of tissue such as bone, fat and water (43). This also emphasizes the importance of correcting for the amount of cerebrospinal fluid (CSF) within the voxel of interest which is not always done. Furthermore, discrepancies in findings between studies could be related to the methods used for analyzing the data. Some studies reported absolute metabolite concentrations whereas others reported ratios with creatine. Although creatine is a relative stable metabolite and these ratios are considered to have good intra-subject validity, between subjects validity of creatine ratios have been questioned because a decrease in creatine with increasing age has been reported in patients with schizophrenia (44) but not in controls (44,45).

When interpreting the findings described in the separate chapters, some limitations have to be taken in to account. First, with the exception of **chapter 7**, the sample sizes of the conducted studies were modest, which could have led to insufficient power and subsequently type II errors. Furthermore, the heavy cannabis users **(chapters 5 and 6)** used other substances (alcohol, nicotine and recreational drugs) in addition to cannabis thereby confounding the effects of cannabis use. Moreover, despite instructions to refrain from substance use 24 hours prior to participation, a few subjects with a psychotic disorder **(chapters 3 and 4)** tested positive on a urine drug screening. Although analyses were repeated without these particular subjects and yielded comparable results, possible

confounding effects of substance use cannot be ruled out. Finally, the inclusion criteria may have caused a selection bias. In **chapters 3** and **4**, we included medication-free psychotic subjects. Although this has the important benefit of eliminating acute confounding effects of antipsychotic drug use, this may have led to a selection bias of relatively well functioning psychotic subjects thereby limiting generalizability of our findings. In **chapters 5** and **6**, at baseline heavy cannabis users without a history or present diagnosis of substance use disorders were included. Since heavy cannabis use was defined at baseline as using cannabis at least 10 days per month for at least two years, we may have selected a group of well-functioning cannabis users which could partially explain the negative findings in **chapter 5**.

Clinical implications and future directions

All studies described in this dissertation have been carried out with the aim of increasing knowledge about neurobiological mechanisms underlying cognitive symptoms of psychotic disorders and substance use disorders in order to contribute to the development of new, effective treatment and prevention strategies. Although there is still much unknown and we have a long way to go before we have unraveled these complex mechanisms, the studies described in this dissertation have provided new insights which could benefit clinical practice and give rise to further research.

First, the studies reviewed in **chapter 2** outline that distinct domains of cognition are modulated via different neurobiological mechanisms. Therefore, future studies investigating neurobiological mechanisms of cognitive impairment in psychosis should differentiate between separate cognitive domains. Regarding clinical practice, these findings plead for a more individually oriented treatment approach given the highly heterogeneous (cognitive) profile of psychotic disorders instead of a protocol based approach. Although protocols and treatment guidelines are useful, these findings highlight the need for extensive mapping of the individual profile and to accordingly adjust the treatment approach. However, development of pharmacological agents with a selective mechanism of action has been proven difficult given the interaction between different neurobiological systems. Nevertheless, several add-on pharmacological agents were found to effectively enhance different cognitive domains and their use in clinical treatment warrant further investigation. The Research Domain Criteria (RDoC) approach could be suitable for this purpose. RDoC refers to a framework for new ways of studying mental disorders, including psychosis, which integrates multiple levels of information ranging from self-report to genetic and biological markers in order to

better understand basic dimensions of functioning underlying both normal and abnormal behavior. The studies described in **chapters 3** and **4** provide further evidence of a role for the cholinergic system in attention, reasoning and problem solving and memory, implying that pharmacological interventions targeting this system can improve these cognitive domains in psychosis. Future studies should further investigate this in a sample of more severely cognitive impaired patients diagnosed with schizophrenia to further investigate altered cholinergic markers in psychosis. Nevertheless, psychotic patients may benefit from interventions targeting the mAChRs and nAChRs. Indeed, previous studies using $M_{1/4}$ receptor agonist xanomeline already showed improvement in memory as well as psychotic symptoms in schizophrenia patients (46). However, xanomeline also produced several side effects. Contrary, studies using acetylcholinesterase inhibitors, which are mainly prescribed for treatment of Alzheimer's disease, did not yield positive results in schizophrenia (47–49). Therefore, the M_1 receptor subtype in particular could be value target for memory enhancement as is it may produce less side effects due to its relative low expression in the peripheral nerve system.

With regard to substance use disorders, the predictive relation between putamen activity and cannabis use related problem severity described in **chapter 6** suggest that habit formation should be a focus point in the treatment of cannabis use disorders. Increased putamen activity in response to cannabis cues seems already to be present in early stages of cannabis use and could therefore be of use in preventing a transition from recreational use to dependence. However, despite the fact that fMRI is a reliable technique to measure group differences, it is not suitable for detecting aberrant activation patterns at the individual level. Yet, advances in new, quickly developing techniques such as machine learning may be able to change this in the future (50). Nevertheless, given the relative small sample we used our findings should be replicated in a bigger sample. Moreover, future studies should also investigate whether cue-reactivity also predicts a transition to cannabis addiction.

In addition to identifying risk-factors, identification of protective factors could also make a valuable contribution to the development of effective treatment and prevention strategies for substance use disorders. The observation of a decreased risk for substance use and substance use disorders in patients with 22q11DS (**chapter 7**) indicates that 22q11DS may be a valuable model to study both genetic factors underlying substance use disorders as well potential protective environmental factors. Moreover, 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 schizophrenia.

To conclude, the studies described in this dissertation have provided new insights in the neurobiological mechanism underlying cognitive functioning in psychotic subjects and substance use disorders. Although these findings are just small pieces of a large and highly complex puzzle, these pieces are important for completing this puzzle in the future.

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Chapter | 9

Summary in Dutch | Nederlandse samenvatting

Nederlandse Samenvatting

Het overkoepelende doel van dit proefschrift was om meer inzicht te verkrijgen in de onderliggende neurobiologische mechanismen van co-morbide cognitieve symptomen bij psychose en aanhoudend, frequent middelengebruik. In het eerste deel van dit proefschrift werden neurobiologische mechanismen die ten grondslag liggen aan cognitieve symptomen bij personen met een psychotische stoornis onderzocht (hoofdstuk 2 - hoofdstuk 4), met een focus op de rol van het cholinerge systeem. In het tweede deel van dit proefschrift werden onderliggende neurobiologische mechanismen van middelengebruik onderzocht met een focus op onderliggende mechanismen van frequent cannabisgebruik (hoofdstuk 5 - hoofdstuk 7).

In **hoofdstuk 2** werd de effectiviteit van farmacologische interventies onderzocht voor afzonderlijke cognitieve domeinen, die over het algemeen aangedaan zijn in patiënten met schizofrenie, zoals bepaald door het MATRICS-initiatief. De bestudeerde studies vonden bewijs voor een rol van de dopaminerge D_1 receptor bij de informatieverwerkingssnelheid en het logisch redeneren alsook het probleemoplossend vermogen. Het serotonerge, GABA-erge en glutamaat systeem lijken betrokken te zijn bij verschillende aspecten van geheugen. Dit laatste systeem lijkt ook betrokken te zijn bij logisch redeneren en probleemoplossend vermogen. Ten slotte werd aannemelijk gemaakt dat aandacht en alertheid gemoduleerd wordt door nicotinerge-acetylcholine receptoren. Echter resultaten van een beperkt aantal studies gaven aan dat geheugenfuncties mogelijk verbeterd kunnen worden door middelen die het muscarine systeem beïnvloeden. Over het algemeen toonden deze bevindingen aan dat er verschillende mechanismen ten grondslag liggen aan afzonderlijke aspecten van cognitie. Als dit inderdaad het geval is, impliceert dit dat patiënten met schizofrenie met verschillende cognitieve profielen baat zouden kunnen hebben van verschillende interventiestrategieën.

In **hoofdstuk 3** werd de rol van de muscarine M_1-receptor in cognitieve functies bij personen met een psychotische stoornis onderzocht met behulp van de M_1-antagonist biperideen als een farmacologische challenge. Het blokkeren van de M_1 -receptor verminderde significant zowel het visueel als verbaal leren en geheugen, hetgeen aangeeft dat deze receptor een rol speelt in deze cognitieve (dys)functies. Verder werd een interactie-effect gevonden tussen medicatie en groep voor logisch redeneren en probleemoplossend vermogen; in de psychosegroep

verbeterde dit domein na toediening van biperideen, terwijl prestatie op dit domein in de gezonde controle groep juist verslechterde na biperideen toediening. Het effect van M_1 -antagonisme op dit domein was dus verschillend voor beide groepen. Het effect van biperideen op de andere cognitieve domeinen was echter vergelijkbaar in de psychose- en de gezonde controlegroep. Hoewel deze resultaten de rol van de M_1-receptor in geheugen bevestigt, geeft het gebrek aan een verschillend effect van M_1-blokkade tussen de groepen mogelijk aan dat het disfunctioneren van de M_1-receptor niet aanwezig was in onze steekproef. Het sluit echter niet uit dat dit wel aanwezig is in oudere, chronische patiënten met schizofrenie.

Hoofdstuk 4 geeft een toelichting op de rol van het cholinerge systeem in psychose en geassocieerde cognitieve stoornissen. We onderzochten of choline concentraties in de anterior cingulate cortex (ACC) en het striatum verschilde tussen personen met een psychotische stoornis en controles, en of blokkade van de M_1-receptor de choline concentraties in deze gebieden beïnvloedde. Daarnaast werd onderzocht of choline concentraties geassocieerd waren met afzonderlijke domeinen van cognitie. Aangetoond werd een significante negatieve correlatie tussen aandacht en choline in het striatum bij psychotische personen die afwezig was bij controles, hetgeen eerdere bevindingen van de rol van het cholinerge systeem in cognitieve symptomen van psychose bevestigt. Het ontbreken van een significant verschil in choline concentraties tussen beide onderzochte groepen, zowel na biperideen als placebo, en in beide hersengebieden, geeft mogelijk aan dat er geen ernstige cholinerge afwijkingen aanwezig waren in deze steekproef van psychotische personen, hoewel we niet kunnen uitsluiten dat er cholinerge afwijkingen aanwezig zijn bij chronische schizofreniepatiënten.

In **hoofdstuk 5** werd de relatie tussen het functioneren van het werkgeheugennetwerk en aanhoudend, frequent cannabisgebruik onderzocht in een longitudinale drie jaar durende functionele MRI-studie. Bij de aanvangsmeting werd bevonden dat, ondanks een vergelijkbaar werkgeheugennetwerkfunctie en prestatie op een werkgeheugentaak (gedragsmatig) in zware cannabisgebruikers en gezonde niet-gebruikende controles, een sterker werkgeheugen netwerkreactie geassocieerd was met verhoogd wekelijks cannabisgebruik over een periode van zes maanden. De follow-up resultaten lieten zien dat, ondanks verbeterde prestatie op de werkgeheugentaak in beide groepen, werkgeheugennetwerkfunctie niet veranderde over de periode van drie jaar. In tegenstelling tot eerdere bevindingen werd er geen significante associatie

gevonden tussen het functioneren van het werkgeheugennetwerk tijdens de aanvangsmeting en cannabis-, nicotine-, alcohol- of ander recreationeel drugsgebruik. Deze resultaten geven aan dat aanhoudend cannabisgebruik het functioneren van het werkgeheugennetwerk niet significant beïnvloedt.

Voortbordurend op eerdere bevindingen van verhoogde activatie in reactie op cannabisstimuli in het ventrale tegmentumgebied (VTA) in zware cannabisgebruikers in vergelijking met controles, alsmede een hogere activatie in de ACC, orbitofrontale cortex (OFC) en striatum in meer problematische cannabisgebruikers, werden in **hoofdstuk 6** de resultaten van een follow-up studie beschreven waarin werd onderzocht of hersenactiviteit in reactie op cannabis gerelateerde stimuli in deze hersengebieden voorspellend was voor veranderingen in wekelijks cannabisgebruik en de ernst van aan cannabis gerelateerde problemen. Geen van de onderzochte gebieden voorspelde wekelijks cannabisgebruik na drie jaar. Echter, verhoogde activatie in het linker (dorsale) striatum voorspelde de ernst van aan cannabis gerelateerde problemen na drie jaar, wat aangeeft dat cue-reactiviteit mogelijk een bruikbaar hulpmiddel is in het voorspellen van de transitie naar problematisch cannabisgebruik en mogelijk ook cannabisafhankelijkheid.

In **hoofdstuk 7** werd de prevalentie van middelengebruik en middelen gebonden stoornissen in 22q11.2 (22q11DS) deletie syndroom, een populatie met een hoog risico op het ontwikkelen van psychotische stoornissen, bepaald. De deletie op chromosoom 22q11.2 die deze groep patiënten definieert, bevat genen die zijn geassocieerd met zowel psychotische stoornissen als middelen gebonden stoornissen. Derhalve kan het onderzoeken van patronen van middelengebruik bij deze patiënten mogelijk waardevolle inzichten geven in de genetische aspecten van zowel psychose als middelen gebonden stoornissen. Vergeleken met psychotische patiënten (88%) en gezonde controles (82%), was de prevalentie van algemeen middelengebruik (37%) en middelen gebonden stoornissen (1.2%) laag in 22q11DS-patiënten. Bovendien vonden we dat deze patiënten een *verlaagd* risico hebben op zowel algemeen middelengebruik als alcohol- en nicotinegebruik afzonderlijk. Interessant is dat recreationeel drugsgebruik niet verschilde tussen de drie groepen. Daarnaast werd binnen de groep 22q11DS-patiënten geen relatie gevonden tussen de prevalentie van middelengebruik en psychose, COMT-genotype en intelligentie quotiënt (IQ). Vergelijkbaar met bevindingen in de algemene populatie was middelengebruik gebruikelijker bij mannelijke dan vrouwelijke 22q11DS-patiënten. Vervolgonderzoek naar zowel neurobiologische

als omgevingsfactoren die bijdragen aan dit verlaagde risico op middelengebruik en aan middelen gebonden stoornissen in 22q11DS is nodig, aangezien dit nieuwe inzichten kan geven in de genetische aspecten van aan middelen gebonden stoornissen bij zowel psychotische patiënten als de algemene populatie.

Concluderend hebben de studies van dit proefschrift nieuwe inzichten gegenereerd in de neurobiologische mechanismen die ten grondslag liggen aan co-morbide cognitieve symptomen in psychose en aan middelen gebonden stoornissen. Echter, deze studies hebben ook nieuwe vragen opgeroepen en vervolgonderzoek is nodig om deze vragen te beantwoorden en de verkregen inzichten te vertalen naar de klinische praktijk.