Chapter 9

Summary and Discussion
COGNITIVE FUNCTIONING IN SCHIZOPHRENIA: STRUCTURE AND CLINICAL CORRELATES

The aim of this thesis was to increase our understanding of cognitive functioning in schizophrenia. Most of the studies were conducted within the framework of the Genetic Risk and Outcome of Psychosis (GROUP) project (chapter 2). We investigated which underlying mechanisms can be held responsible for impairments in working memory (chapter 3), and reasoning/problem solving (chapter 4). Determinants of heterogeneity in cognitive task performance were studied by relating the cognitive subtype of the unaffected sibling to their affected family member (chapter 5). Next, we investigated the characteristics of profiles of premorbid adjustment and their relationship with cognitive functioning (chapter 6). Finally, we investigated the relevance of cognition for illness insight, with specific attention paid to the role of social cognition (chapter 7 and 8).

Genetic Risk and Outcome of Psychosis (GROUP)
In chapter 2, we presented the objectives, sample characteristic, recruitment and assessment methods of the GROUP project, a multi-site longitudinal cohort study focused on gene-environment interaction in psychotic disorders. What makes the GROUP project unique compared to other studies is the inclusion of a large sample of young patients (N=1120), their unaffected siblings (N=1057), parents (N=919) and unrelated controls (N=590). Inclusion of these four cohorts allows for unique comparisons, which may improve our understanding of the aetiology, course, and outcome of schizophrenia and related disorders. Results of the cognitive assessment at baseline have been described in another study (Meijer et al., 2011).

Cognitive Functioning in Schizophrenia
It has been well established that cognitive impairments are a highly prevalent feature of schizophrenia. Based on factor analysis, seven domains have been found to be of importance: ‘processing speed’, ‘attention/vigilance’, ‘working memory’, ‘verbal learning/ memory’, ‘visual learning/memory’, ‘reasoning/problem solving’, and ‘social cognition’ (Nuechterlein et al., 2004). For each of these domains, multiple performance-based tasks have been described.

It is not fully understood which underlying mechanisms are responsible for the impairments on the domains described. Two cognitive domains were investigated in more detail: working memory (chapter 3) and reasoning/problem solving (chapter 4). Working memory involves the mental maintenance (short-term storage and rehearsal) and manipulation of verbal and visuospatial information. We showed that performance differences between patients and controls were already present in a control condition that required only minimal involvement of the maintenance and manipulation components (chapter 3). Performance differences increased only when maintenance and manipulation demands increased simultaneously. We suggested that performance differences in the control condition were attributable
to perceptual strategies, whereas the increase in differences in the “maintenance-plus-manipulation” condition was suggested to be influenced by cognitive capacity. This indicates that other factors may play a role in working memory task performance. In addition, performance impairment may not only be attributable to brain areas involved in executive function (e.g. the prefrontal cortex).

Another cognitive domain within the executive functions is reasoning and problem solving. Tasks measuring this domain typically require mental flexibility, reasoning, or visuoconstruction (Nuechterlein et al., 2004). Such tasks are known to reflect higher order cognitive abilities. It remains to be elucidated whether the problems in mental flexibility are the result of a general cognitive impairment, or whether they represent a discrete area of vulnerability. In the current thesis, we investigated mental flexibility into more detail, using two tasks measuring either explicit or implicit processes of set-shifting (chapter 4). Task performance was only modestly related to indices of general cognitive functioning, suggesting that it measures fairly discrete cognitive processes. Patients with psychotic disorder did not show diminished flexibility when shifts in task rules are procedural (implicit), but were less flexible when explicit rules for responding change. Not all patients were impaired on the set-shifting task. Patients showing more set-shifting impairment also showed more disorganized speech and behaviour, and more emotional discomfort.

**Contributors to Cognitive Impairment**

We then shifted our attention to the determinants of cognitive impairment in patients with schizophrenia (chapter 5). At first glance, it may be thought that psychotic episodes are responsible for cognitive impairment in schizophrenia. However, there is no convincing scientific evidence for this hypothesis (Becker et al., 2010). In addition, cognitive impairments have also consistently been reported in first-degree relatives. This indicates that the cognitive impairments in schizophrenia cannot be solely attributed to the influence of disease-related factors, such as psychotic episodes, hospitalization, unemployment, or medication effects. Rather, they may represent genetic risk for development of psychosis. Cognitive profiles in unaffected siblings have been found to be of a similar structure as those of their affected family member. Various cognitive profiles have been suggested in schizophrenia, but these have never been studied in unaffected siblings. We therefore investigated cognitive subtypes in siblings, their characteristics, and compared these with the proband (their affected family member). We found three subtypes in siblings: normal, mixed, and impaired. Siblings with an impaired profile had more subclinical psychotic symptoms, and poorer social functioning. Surprisingly, the poorer the cognitive profile of the sibling, the higher the level of correspondence with the cognitive profile of their proband. In addition, the siblings’ cognitive subtype was predictive of disease course in the proband. The probands of siblings with cognitive impairment were overall more impaired than the probands of siblings with a different profile. However, these patient groups showed the same relative
pattern of impairment across cognitive domains, with the greatest impairment in verbal learning and memory, and processing speed, and the least impairment in visuoconstruction and verbal comprehension. Distinguishing between cognitive profiles in unaffected siblings may be of relevance for genetic studies. Also, the increased expression of endophenotypes in certain cognitive subtypes may be of importance for the development of more specific pharmacological drugs, and possibly for predicting which siblings are at risk of psychosis. Of note, many of the siblings did not show an abnormal cognitive profile, and showed no signs of subclinical symptoms. Thus, being a sibling of a patient with psychosis does not necessarily increase the risk for future development of psychosis.

Different developmental pathways may precede the first psychosis, long before the first signs of the illness become observable. In chapter 6, we evaluated social and academic adjustment from childhood to late adolescence, using a commonly used retrospective questionnaire. Cluster analyses resulted in six different profiles of premorbid adjustment in patients: normal, social intermediate, academic decline, overall decline, overall intermediate, and overall impaired. In line with what one would expect, patients with a normal premorbid profile were functioning at higher levels, as compared to patients with maladjustment already during childhood. Interestingly, the patients displaying a decline in functioning more often had a history of substance disorder (cannabis). They were also more likely to be male. The patients with a normal or social intermediate profile had the highest levels of intellectual function. However, as with the previous chapter, the profiles showed the same relative pattern of performance across cognitive tasks. Based on the premorbid profile of the patient, we also found differences between their unaffected siblings, but less between their unaffected parents. Presence of premorbid maladjustment in the patient did differentiate between characteristics in siblings (subclinical symptoms, early adjustment), but this effect was not as large as in the patient. In addition, this effect was irrespective of the patient profile. We concluded that presence of premorbid maladjustment in patients is associated with familial liability, presumably the result of shared genetic and environmental factors of the sibling with the patient.

Cognition and Insight
One may think of several consequences impaired cognition can have for the patient’s life. Perhaps the most urgent is that impaired cognition hampers return to work (Nuechterlein et al., 2011). But impaired cognition may also have other consequences. Patients with more cognitive impairment may report less complaints, and their account may differ from their family members and other caretakers. Reduced insight has been found in the majority of the patients with a psychotic disorder. Insight in psychosis is a complex, multidimensional construct, and is likely to be influenced by multiple factors. Many studies have found a relationship of insight with traditional cognitive aspects (e.g. attention, working memory), neglecting the role of social cognition (e.g. emotion perception, theory of mind). Social
cognition can be defined as “the ability to construct representations of the relations between oneself and others and to use those representations flexibly to guide social behaviour” (Adolphs, 2001). A difficulty in adopting other mental perspectives, i.e. with seeing the world as others do, may particularly be associated with understanding one’s own condition (David, 1999). A number of studies have found social cognition to be related to insight (Langdon et al., 2009; Bora et al., 2007), but these studies did not correct for the contribution of traditional cognitive aspects. In chapter 7, we found that deficits in social cognition show a unique relationship with insight, over and above the role of other cognitive aspects. Therefore, next to attending, memorizing and planning, successful perception and interpretation of social-emotional information may be required for insight. We also studied whether patients with more cognitive impairment were less able to improve their insight over time. Studying the natural course of insight (chapter 8), we found that patients having better cognitive abilities and fewer clinical symptoms at baseline were more likely to be improved in terms of insight after three years.

Implications for Future Research
The GROUP project, set up in 2004, is one of the largest multi-site studies of schizophrenia to date. The current thesis primarily focused on the baseline results of this study, with a specific focus on cognitive functioning, its structure, and clinical correlates. The duration of the cognitive battery was approximately one hour per subject, and thereby it compromised a large part of the total assessment time. Cognitive tasks loading on previously described and validated domains were selected for inclusion in the battery (Nuechterlein et al., 2004).

Heterogeneity was a common denominator for performance of patients on experimental tasks, awareness of illness, premorbid adjustment, and even for cognitive functioning in unaffected siblings. For future studies, it may be beneficial to investigate profiles of patients, since these are based on multiple instead of single characteristics. This may lead to more homogeneous subtypes, which can contribute to our understanding of the etiology of schizophrenia and related psychoses. The patients had a cognitive profile that was in line with earlier findings (Palmer et al., 2009). The structure of this profile persisted in the subgroups, which were based on cognitive functioning of the unaffected sibling (chapter 5), and premorbid functioning of the patient (chapter 6). From the current thesis it follows that for clinical neuropsychological evaluations, it may not yet be possible to characterize a cognitive profile that uniquely fits to all patients with psychosis. For the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, it has been proposed to describe cognitive impairment in schizophrenia and related psychoses in terms of severity (http://www.dsm5.org/ProposedRevision). Such a quantification may be the best way to describe cognitive impairment, for the time being.

As has been found in earlier studies, a portion of the patients performed within ‘normal limits’. However, this does not mean that they are neuropsychologically normal. Viewing
the GROUP baseline results on the cognitive battery, patients consistently performed at poorer levels, as compared to their unaffected siblings (Meijer et al., 2011). In addition, the best performing patients in chapter 5 had siblings with far better performances. So, some patients may show performance levels within normal limits, but nevertheless perform below their expected levels. In certain situations, the availability of assessing an unaffected sibling may be of benefit in order to compare the patient with an estimated profile of cognitive functioning, and possibly, this may give the clinician more information about the course of illness in the patient.

It should be noted that similarities in structure of cognitive functioning do not indicate similar underlying genetic and environmental factors. In patients showing decline in premorbid adjustment, cannabis sensitivity may play a more prominent role, and may result in cognitive impairment. In patients with early maladjustment, genetic and perinatal factors may cause developmental arrest of cognitive function. Using profiles, we were able to confirm that cognitive impairments are not solely the result of disease-related factors (e.g. medication effects). Future studies should investigate the longitudinal course of profiles into more detail. For example, it would be interesting to study whether the profiles characterized by decline in adjustment are accompanied by progressive cognitive decline, found in a subgroup of patients (Andreasen et al., 2011). Further, the familial factors that are linked to premorbid adjustment in patients need to be studied in more detail. The GROUP project is currently analysing data on the follow-up assessments. These can be used in order to address a number of the abovementioned questions, which may contribute to our understanding of schizophrenia.

A number of limitations of the current thesis should be noted. Firstly, our cognitive battery was comprehensive, but not complete. A measure of visual learning was not included. Also, a number of the cognitive domains were indexed by single tests. In some cases, this may lead to data interpretation problems. For instance, it is well-described that the WAIS-III Digit Symbol Coding task not only measures processing speed, but also working memory, visual scanning etc. For an adequate assessment of processing speed, this problem may have been circumvented would we had included other tests to index this domain (i.e. the Trail Making Test – A).

It may also be possible that we have overlooked other issues in the interpretation of our results. It has been suggested that task performance of schizophrenia patients on more challenging cognitive tasks is influenced by ‘energetic’ processes, next to computational (or normal information) processes (Gorissen et al., 2004; Schmand et al., 1994; Granholm et al., 2007). Applying this theory to the outcomes of chapter 3, energetic processes would explain the performance decrement of the patients on the ‘maintenance-and-manipulation’ condition. They would also explain the poorer performances of patients on more cognitively demanding tasks such as the WAIS-III Digit Symbol Coding. However, only a few studies have investigated energetic processes in schizophrenia. The border between the theoretical
concepts called ‘energetic’ and ‘computational’ processes can in reality be more diffuse, as it has not been ruled out that these processes have a similar neurobiological basis. For example, one of the causes of failure in energetic processes has been suggested to be the ‘frontal lobe syndrome’ present in schizophrenia patients (Gorissen et al., 2004). The same syndrome may explain failure of computational processes as well. In addition, it remains unclear how energetic processes would explain cognitive alterations in non-affected relatives. Energetic processes contributing to poor neuropsychological task performance in schizophrenia need further verification.

Much progress is currently being made in the development of new cognitive tests for schizophrenia research (Nuechterlein et al., 2011; Gold et al., 2011). Many of these new cognitive tests were not yet available at the time of the baseline assessment of the GROUP study. For future genetic studies, it may be interesting to include more experimental tasks, such as the Response Set-shifting Test, and the Delayed Matching-to-Sample Test. These tasks have the advantage that they measure more discrete functions, which could address the problem of heterogeneity in schizophrenia more adequately.

**Implications for Treatment**

Given the high prevalence of cognitive impairment in schizophrenia and its substantial impact on outcome, treating cognitive impairment has received increased attention during the last several years (Nuechterlein et al., 2011; McGurk et al., 2007). So far, pharmacological treatments have had limited success in improving cognitive function in schizophrenia (Rund and Borg, 1999; Marder, 2006). Cognitive remediation (CR) is a psycho-social intervention which is specifically focused on cognitive processes (e.g. attention, verbal learning and memory, executive functioning), and intends to improve functioning at the level of cognitive performance, daily living, or vocational skills (NICE, 2009). A range of CR studies have been conducted during the past 40 years, and these have used different treatment approaches. A substantial number of the CR studies for schizophrenia patients have shown improvements on cognitive measures. However, there is too little evidence to conclude that CR improves functional outcome (NICE, 2009; Dixon et al., 2009; NVvP, 2012), although it may be effective in combination with psychosocial rehabilitation (McGurk et al., 2007). An exception to this is Cognitive Adaptation Training, a program that uses environmental supports to bypass cognitive impairments (Velligan et al., 2000; Velligan et al., 2002; NICE, 2009). The official guidelines for the treatment of schizophrenia do not yet recommend CR as an effective intervention (Dixon et al., 2009; NICE, 2009; NVvP, 2012).

Nevertheless, the current thesis offers several opportunities for the treatment of individuals with schizophrenia and related psychotic disorders. With regard to working memory (WM), treatments may need to incorporate methods that reduce the impact of WM impairment. For instance, during psycho-education, new information presented verbally may need to be supported using visual material (e.g. hand-outs, posters). Clinicians may also
consider reducing their rate of instruction, leaving more cognitive space left for information processing. Some of the patients with schizophrenia also show mental flexibility problems. These patients may benefit from a higher level of structure (i.e. stable living environment, fixed appointments, and schedules).

Profiling patients may ultimately lead to more individualized treatments of patients with schizophrenia, and other psychiatric illnesses. A profile of cognition may help to identify patients eligible for a CR treatment programme. It can also inform the clinician, family member, or other actors about the relative strengths and weaknesses of the patient. Patients with cognitive functioning within normal limits may have a less chronic course, and may therefore need a different treatment approach. Profiling by premorbid adjustment can be of benefit to identify individuals at a higher risk for future development of psychosis. For instance, individuals with rapid decline in academic functioning may require remedial teaching, in order to graduate from school. Individuals with social decline may benefit from peer support groups, or other psycho-social interventions.

Treatments that aim to improve insight need to consider the patients’ cognitive functioning, in addition to clinical symptoms. Hypothetically, improving cognitive functioning and decreasing clinical symptoms may ultimately lead to improvements of insight over time. It may also be possible to target these factors together with insight in one treatment. An example of such a multi-faceted treatment program is called REFLEX (Pijnenborg et al., 2011).

To conclude
The current thesis describes a number of new findings on cognitive functioning in schizophrenia and psychoses. Working memory impairment is more than the sum of its components. Explicit set-shifting mechanisms are the major contributor for the loss of mental flexibility. Unaffected siblings vary largely in their cognitive functioning. The more cognitively impaired the unaffected sibling, the more they resemble the cognitive profile of their affected family member. This yields possibilities to study the genetic underpinnings of cognitive endophenotypes in more detail. Heterogeneity characterizes the premorbid trajectories leading to the onset of the first psychosis. Profiling premorbid adjustment in patients adds predictive value to later cognitive functioning and disease severity. To gain more insight into insight, it is pivotal to take into account – next to clinical symptoms and traditional aspects of cognition - social cognition. Finally, the persistence of impaired insight cannot be ascribed merely to the traditional cognitive aspects.