Chapter 7

Summary and general discussion

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At present it has no doubt that cognitive deficits play a role in schizophrenia. There is however less consensus about their cause, nature and outcome. The studies presented in this thesis focused on the nature and outcome of cognitive deficits in schizophrenia. In chapter two the heterogeneity in cognitive performance in schizophrenia is examined. Chapter three investigated the claim that frontal, or rather executive, impairment is a core deficit in schizophrenia. Chapter four is concerned with the mutual relations between cognitive functions in schizophrenia, with the focus on memory problems. In chapter five the relation between cognition and psychopathology was investigated. Finally, chapter six reported on the influence of cognition on outcome. In this final chapter the results of these studies are compared with the most important findings in the literature to see whether this could unravel a part of the puzzle.

1. Cognition and schizophrenia

The results presented in chapters two, four and six showed that schizophrenia patients as a group performed below the level of healthy controls on almost all cognitive tasks, except for the storage of verbal information and selective attention. The largest impairments were found for general verbal learning and speed of information processing. This is to a large extent in accordance with the results of a large meta-analysis on cognition in schizophrenia, which reported the largest impairments on global verbal memory and performance IQ (Heinrichs and Zakzanis, 1998). It is well known that performance IQ has a strong speed component. The relatively spared storage of verbal material is also often reported (e.g. Aleman et al., 1999).

A discussion about cognitive deficits cannot ignore the special role which executive or “frontal” deficits are supposed to play in schizophrenia. These terms are often mixed up, because the frontal lobes are presumed to mediate executive functioning. Because of the resemblance between patients with frontal lobe lesions and patients with schizophrenia (e.g. Benson and Stuss, 1990) research into frontal or executive functions in schizophrenia received a lot of attention. In this thesis several cognitive tasks, which appeal to executive

functions were used: the double stimulus version of the Continuous Performance Task (CPT), Stroop interference, Trailmaking Test interference and Verbal Fluency. In chapter three two experimental methods were used as well, the antisaccade task and the memory saccade task. On three of these tasks, CPT signal detection, Verbal Fluency and the antisaccade inhibition task, patients differed significantly from healthy controls. These differences were less pronounced for Stroop interference and memory saccade errors and no significant differences were found on the Trailmaking Test inference score. These results do not support the idea of a dysexecutive syndrome as the core cognitive deficit in schizophrenia.

There is a distinction between the performance on a task and the underlying cognitive function. Most tasks depend on several cognitive functions or constructs. Mutual correlations between several different cognitive tasks can shed some light on this matter. Correlations between cognitive tasks, presented in chapter four, demonstrate that both signal detection on the CPT and Verbal Fluency correlated strongly with speed of processing measures, while this was less pronounced for Stroop interference and absent for Trailmaking interference. The antisaccade task in chapter three only correlated with speed of processing measures and signal detection on the CPT. This could suggest that speed of processing rather than executive functions play an important role in the differences between patients and healthy controls on these tasks. Of course it is still not known what "processing speed" is in neurophysiological terms. It is not unlikely that speed of processing reflects executive processes on a very short time interval, responsible for the efficiency of our information processing.

2. Cognitive heterogeneity in schizophrenia

Although schizophrenia patients, as a group, show specific cognitive deficits against a background of general cognitive dysfunctioning, there are large inter-individual differences. In chapter two a group of patients with normal cognitive performance according to clinical norms was identified. In chapter three patients were classified according to the cognitive deficits on both cognitive and saccadic tasks. The idea that this diversity is caused by the existence of different subgroups cannot be corroborated on the basis of the results presented in

chapter two. No differences were found between patients with and without cognitive deficits on obstetric complications, premorbid adjustment, age at onset, psychopathology and substance abuse. The only difference was in social functioning, in particular on the occupational role, which is a consequence rather than a cause of differences in cognitive performance. Although the "cognitively normal" patients performed within clinical limits, as a group their performance was below the level of healthy controls and their profile was more or less the same as that in "cognitively impaired" patients. Twenty-four percent of the healthy controls also showed cognitive deficits according to clinical criteria. This is in accordance with other studies showing that a part of the normal controls also exhibit cognitive deficits (e.g. Palmer et al., 1997). An interesting question would be whether these cognitively impaired controls show the same subclinical profile as the patient group. This could mean that cognition in general should be viewed as a dimensional phenomenon lying on a continuum with normal performance. It could also point to a bias in testing by which certain specific deficits show up because some tests are more difficult than others (Chapman and Chapman, 1978). A closer look at the mean z-scores of the cognitively impaired controls showed that this was not exactly the case. They were most disturbed on verbal encoding and selectivity of attention, while the patients as a group had most difficulty with speed of information processing and verbal encoding. A model in which separate cognitive dimensions are seen as discrete but interrelated dimensions seems more plausible. It could be hypothesized that the dimensions of verbal encoding and speed of processing play a special role in schizophrenia.

In chapter four the association between several explicit long-term memory processes and speed of processing was examined to see whether the memory deficits in schizophrenia are primary deficits or secondary to a slowing in processing speed. Although speed reduced part of the disease related variance in memory, it did not explain all the differences between patients and controls on long-term memory tasks. A dimensional approach also leaves room for research into other risk or protective factors, which modulate the expression of these cognitive dimensions. Compensation capacity, for example, could be a protective factor. The term compensation is often used in dementia research in which context Satz (1993) developed the Brain Reserve Capacity (BRC) theory. In short, this theory states that due to environmental enrichment, genetic

predisposition or both, some individuals develop a cognitive reserve that may increase the threshold for cognitive deficits after brain pathology. The study presented in chapter two suggested that this compensation capacity, indirectly measured by intelligence and educational level, could explain why some schizophrenic patients did not show cognitive deficits during neuropsychological assessment. It could be speculated that these risk and protective factors can obscure the relationship between cognition and other domains of functioning in schizophrenia. A dimensional approach on cognitive research in schizophrenia, which also incorporates certain protective and risk factors, seems to be the best approach to unravel the role of cognition in schizophrenia.

3. Different approaches to the assessment of cognition in schizophrenia

Throughout this thesis three separate methods to assess cognitive functioning were used: clinical cognitive tests, experimental saccadic paradigms and a questionnaire of subjective cognitive problems. The correlations between the first two methods were not very impressive. Only a few significant correlations were found. These correlations, however, were rather robust and still significant after a Bonferroni correction. It is also remarkable that the saccadic tasks correlate with the most impaired cognitive measures in schizophrenia, namely speed of processing, vigilance and verbal encoding. This could suggest that these measures represent the most impaired neurocognitive systems in schizophrenia.

The correlations between subjective and objective, or neuropsychological cognitive measures are another story. Only a few correlations were significant, and none of them holds significance after a Bonferonni correction for multiple testing. This is in accordance with the literature in which only marginal correlations between objective and subjective cognitive measures were found (Van den Bosch and Rombouts, 1998; Williams et al., 1984; Zanello and Huguelet, 2001). In chapter five it is suggested that some schizophrenia patients are able to improve their cognitive performance by investing more mental effort, but at the cost of more subjective complaints. This mechanism could

certainly obscure correlations between objective and subjective cognitive measures. It also suggests that subjective measures of cognition or mental effort are useful supplement to cognitive research in schizophrenia.

4. Cognition and antipsychotics

Given the rather extensive literature on the allegedly positive effects of the novel atypical antipsychotics on cognition, no discussion on cognition in schizophrenia is complete without paying attention to this topic. Most articles report a cognitive improvement with atypical antipsychotics (e.g. Harvey and Keefe, 2001; Meltzer and McGurk, 1999). However, this is obscured by a few factors. Firstly, there is a publication bias of industry-sponsored studies reporting positive effects. Secondly, most studies compare the effect of atypical antipsychotics with the effect of high doses of classical antipsychotics. Although some researchers suggest that the effect of classical antipsychotics on cognition is neutral (Green et al., 2002) there is some evidence for subtle adverse effects of classical antipsychotics on cognition (Carpenter and Gold, 2002). While normal persons, for example, show practice effects on repeated cognitive tests, this improvement is not manifested in clinical trials of classical antipsychotics with schizophrenia subjects. There is also some evidence for motor slowing due to the extrapyramidal effects of (high dosed) classical antipsychotic drugs (Mortimer, 1997). Moreover, when cognitive performance of patients receiving atypical antipsychotics is compared with patients receiving low doses of classical drugs, no differences are found (Green et al., 2002).
Thirdly, the results are also biased by the addition of anticholinergic drugs, to suppress extrapyramidal side effects of classical antipsychotics, which can negatively influence memory performance. In conclusion, there is hardly any evidence for a positive effect of atypical antipsychotics on cognition. Or to quote Carpenter and Gold (2002)”few researchers will consider taking atypical antipsychotics themselves, or describe them to patients with dementia in order to improve cognitive functioning.”
Does this have any consequences for the studies reported in this thesis? In order to answer this question extra analyses have been performed on the data of the Dutch multicenter study on first episode schizophrenia (see chapter 2, 4 and 6).

In this total group, twenty-five patients used classical antipsychotics, seventy-five used atypical antipsychotics and eighteen patients did not use antipsychotics, during cognitive assessment at inclusion. Most of the medication free group refused to take medication. No significant differences between these three groups were found on PANSS psychopathology dimensions or general social functioning. The medication free subjects in general performed better on all cognitive measures. This was significant for vigilance, speed of processing, Stroop interference and verbal learning.
It seems highly unlikely that they represent a cognitively better subgroup. They only differ from the other group in their noncompliance, probably due to a stronger negative evaluation of subjectively experienced side effects.
There was only one significant difference between subjects with atypical and classical medication. Subjects with atypical medication performed significantly slower on measures of processing speed. Although only ten patients used anticholinergic medication, data concerning the influence of this type of medication on cognitive performance were analyzed as well. Patients with anticholinergic medication performed significantly worse on verbal consolidation and verbal fluency. Although these patients did not participate in a randomized controlled double blind medication trial, the data in this study suggest that the effects of medication on cognitive functions could be negative rather than positive. Neither do they suggest any beneficial effect on cognition of atypical medication above classical antipsychotics. This latter finding probably results from the generally low dose of classical antipsychotics used in this study. Thus it is possible that the cognitive deficits found in schizophrenia are at least partly caused by medication, although this could never be a strong effect. It is not likely that the differences between cognitively “normal” and cognitively impaired patients are caused by medication because no significant differences in medication use were found between these two groups. Neither is an influence of medication expected on the relation between cognition and psychopathology or functional outcome. The same holds for negative effects on saccadic task performance, because animal studies showed that only clozapine, which was not prescribed to the subjects in our study, had a marginal effect on saccadic brain mechanisms. In conclusion, no strong effects of the use of antipsychotic medication on the results presented in this thesis are expected.

5. Cognition and psychopathology

The ways in which the relationship between psychopathology and cognition is investigated has led to different results. In chapter two the question whether patients with more cognitive deficits showed more psychopathology was investigated in a cross-sectional design by comparing the levels of psychopathology between patients with and without cognitive deficits. No significant differences were found. Instead of using multivariate group comparisons, another approach is to study the correlations between dimensional scores of psychopathology and cognitive measures in a cross-sectional design. This was investigated in chapter five and although some correlations between cognitive measures and psychopathology dimensions were found, none of these could stand a Bonferroni correction for multiple testing, meaning that their significance is only marginal. This is in accordance with the inconsistent findings of other cross-sectional studies in the literature both for recent onset and chronic patients. Longitudinal studies with multivariate statistics on changes in cognition mostly yield negative results, even if changes in psychopathology take place (e.g. Rund, 1998). These negative results are not surprising. In view of the large variance of psychopathology and cognition within schizophrenia it could be suggested that it is better to investigate the relationship between psychopathology and cognition by looking at intra-individual changes in both psychopathology and cognition. In recent onset groups positive correlations have been found between clinical improvement and improvement of cognitive performance (Censits et al., 1997; Gold et al., 1999; Hoff et al., 1999). In more chronic patients groups these correlations have not been found (Heaton et al., 2001; Hughes et al., 2002). It is possible that in recent onset schizophrenia some cognitive functions are negatively influenced by the severity of psychopathological symptoms. But this is only a small effect because even if there is an obvious improvement of symptomatology, cognitive impairment still persists.

6. Cognition and outcome in schizophrenia

In schizophrenia research in general two domains of outcome can be distinguished: course of illness and functional outcome. Although the latter is often bracketed together with cognition, few studies looked at the association between cognition and course of illness. In chapter six a significant relation was found between selective attention, verbal fluency and time in psychosis. However, both cognitive measures together only explained five percent of the variance, which is not very impressive. This is in concordance with a study by Verdoux et al. (2002) of the relation between cognitive measures and the recurrence of psychosis in a mixed diagnose group with a first psychosis. This result was also just significant. Cognition did not have any predictive value for course of illness in another study of Robinson et al. (1999). In sum, the predictive value of cognition for course of illness is at most marginal.

Cognition had some limited predictive value for need for care in chapter six. This could reflect the subjective nature of the need for care assessment, by which subjectively experienced cognitive deficits might increase the subjective evaluation of need for care.

In theoretical models cognition is often seen as one of the main causes of social and occupational dysfunctioning in schizophrenia (e.g. Goldman-Rakic, 1994; Cornblatt, 1999). This view is often copied in theoretical reviews (e.g. Holden, 2003; Kuperberg and Heckers, 2000). Usually these statements are based on two quantitative reviews by Green (1996; 2000). A closer look at these reviews shows that the results are mostly based on cross-sectional studies with mixed or chronic patient groups. Moreover most significant correlations between cognition and functional outcome do not stand a Bonferonni correction for multiple testing. In order to study the predictive value of cognition in schizophrenia the most logical choice would be a recent onset group, because such a study would not have a bias towards the inclusion of more chronic subjects with poorer outcome. In the literature to date only one longitudinal prediction study of recent onset patients was found, without any significant results. In our study (chapter 6) neither specific, nor global cognitive measures had any predictive value for social functioning two years after illness onset. Specific cognitive measures did not predict work performance, but having a cognitive deficit in a general sense did. The difference between work

performance and social functioning lies mainly in the importance of interpersonal interactions. It is possible to perform well on certain jobs without having a lot of interpersonal contacts. Obviously the role of cognition in interpersonal contacts is very limited and emotional disturbances or positive or negative symptoms may play a much larger role in social dysfunctioning in schizophrenia. The general influence of cognitive deficits on work performance suggests that cognitive deficits work as rate limiting factors on occupational functioning, possibly in the same sense as physical handicaps can hamper work performance.

7. Cognition and brain dysfunctioning in schizophrenia

One of the most important conclusions which can be drawn from the results in this thesis is that cognitive dysfunctioning is not directly related to other domains of functioning, such as psychopathology or functional outcome, and probably represents a separate dimension in schizophrenia. This makes it hard to maintain the claim that cognitive deficits are the core deficit and probably the cause of schizophrenia. Therefore it would be illogical to presume that the brain mechanisms, which mediate cognitive performance in schizophrenia are the same that cause the disease.

The question remains how to fit the cognitive deficits into the most recent theories and insights concerning brain dysfunctioning in schizophrenia.

Because cognitive tasks are rather indirect measures of brain functioning, we can only speculate on the basis of the results presented in this thesis.

In the past brain research in schizophrenia has been dominated by the concept of localized dysfunctions. Several regions of the brain were put forward as the "site" of schizophrenia: the basal ganglia, the temporal lobes and most of all the frontal lobes. In chapter three the performance of schizophrenia patients on anti- and memory saccadic tasks were compared with healthy controls. Although a number of patients performed significantly worse than normal controls, some patients did not show any deviant performance on these tasks. The brain mechanisms behind saccadic task performance have been examined relatively well. One of the most important regions involved in performance on these tasks is the dorsolateral prefrontal cortex. The existence of a patient group with

normal performance on these tasks could suggest that the involvement of this region is not of crucial importance in schizophrenia. Of course this is speculative, but the results of a large meta-analysis on structural and functional imaging results gives stronger evidence for this claim (Zakzanis and Heinrichs, 1999). This meta-analysis suggests that the average magnitude of difference between patients and controls is generally too modest to support the idea that frontal brain dysfunction is a necessary component of schizophrenia.

Nowadays more and more researchers leave this localistic approach and catch on to the idea that certain circuits in the brain connecting multiple cognitive sites and systems play an important role in the pathopsychology of schizophrenia (Andreasen et al., 1998; Harrison et al., 1998). This is not so far from the localized view because most often circuits connecting the prefrontal cortex, temporal lobe or more specific the hippocampus and certain subcortical areas are proposed to play a crucial role in schizophrenia. It is very well possible that disconnection problems somewhere in these circuits can cause a range of different symptoms and deficits. The memory deficits in schizophrenia for example could be due to a problem in connectivity necessary in the forming of memory traces. Although the neurophysiology of speed of information processing is still unknown, it is likely that "speed" reflects the efficiency by which certain brain areas are employed to complete a simple task. It is possible that problems in connectivity make certain processes less efficient, thereby effecting speed of processing negatively.

This efficiency by which certain circuits work, could also play a role in compensation processes. There is indeed some evidence from functional imaging research, showing that schizophrenia patients show neural inefficiency, which shows as elevated activity on performance-corrected tasks (e.g. Ramsey et al., 2002).

These are all speculations however and schizophrenia is still a disease whose mechanisms are relatively unknown.

8. Conclusion

In sum, cognitive deficits, especially in verbal encoding and speed of information processing are often found in schizophrenia. Contrary to popular

opinion, no apparent evidence is found for specific deficits in executive functions. The most important finding however is that there are large inter-individual differences in cognitive performance in schizophrenia. These differences could not be explained by the existence of different subgroups or by disease severity. Cognition is also not, or marginally related to other domains of functioning, such as psychopathology and social functioning.

The question presents itself whether cognition plays such an important role in schizophrenia that it justifies the large effort in research. The answer is still affirmative, especially since conversation with patients teaches us that most of them have the subjective experience that cognitive deficits play a role in their life. But in order to unravel the role of cognition in schizophrenia conceptual changes have to be made.

Firstly, it seems better to treat cognitive functions as discrete but interrelated dimensions in schizophrenia, without a direct or causal relationship to psychopathology or social functioning. Because of the inter-individual differences it might be better to focus on intra-individual changes and relations with other levels of functioning. Examples of this kind of research are studies on the predictive value of individual changes in cognition in recent onset schizophrenia.

Secondly, protective or risk factors, which can alter the expression of cognitive dimensions, have to be studied as well. A possible protective factor is the compensation capacity, which enables persons to perform at a higher level by investing more mental effort. A possible risk factor could be the initial level of mental fatigue before task performance. Both factors can be studied by using subjective questionnaires on mental effort, mental fatigue and subjectively experienced task load together with the cognitive measures. Or by physiological measures thought to reflect mental effort or fatigue, such as changes in systolic blood pressure or in certain frequencies in heart rate variability. A potential problem of these types of studies is that specific physiological measures are sensitive to the use of specific antipsychotics (Agelink et al., 2001). Also very interesting are functional imaging studies of patterns of compensatory cortical activation on performance corrected tasks.

Thirdly, a lot of patients learn to live with their deficits after a few years and rearrange their lives in order to avoid situations that they cannot cope with. Searching for solitary work, resting a lot in the weekends or having a very

protective partner who takes care of a lot of daily life hassles are examples. Outcome measures do not always take these changes into account, thereby missing confounding factors on the relationship between cognition and outcome.

In sum, both experimental studies on the relations between compensation capacity or mental fatigue and cognition, and large longitudinal studies on the effects of changes in cognition early in the disease on outcome in a more stable phase of the disease, taking confounding factors into account, are interesting directions for future research.

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