Chapter 1

Introduction

1. Schizophrenia

Schizophrenia is a severe psychiatric disease, characterized by a range of dysfunctions in perception, thinking, language, behavior, affect, volition, drive and cognition. No single symptom is pathognomonic for the disease. Psychotic episodes with delusions, hallucinations and often bizarre behavior, combined with disorganized speech and thinking are often alternated with periods in which negative symptoms, such as loss of initiative, flattening of affect and psychomotor poverty are prominent. These signs and symptoms are associated with marked social or occupational dysfunction. The prevalence is approximately 0.5 percent of the total population. The incidence is about 0.2 per thousand inhabitants in the age category of fifteen to forty-five. The worldwide incidence of schizophrenia is remarkably stable and apparently hardly influenced by differences in cultural background (Eaton et al., 1995). The mean age at onset for the first psychotic episode is in the early or mid-twenties for men and in the late-twenties for women. The onset can be acute or insidious and most individuals have some sort of prodromal signs and symptoms such as self-negligence, social withdrawal and flattening of affect. About a quarter of the patients fully recovers after one or two psychotic episodes, half of the patients shows partial recovery with remittent episodes, while the remaining quarter shows a chronic course (Hegarty et al., 1994; Ram et al., 1992). Mortality is high, with a suicide rate of 10 percent. The illness usually reaches a stable level after the first two to five years (Belitsky and McGlashan, 1993). The course of illness in the early phase of the disease is a good predictor for the long-term course (Harrison et al., 1996). Other known factors associated with a good prognosis are good premorbid adjustment, acute onset, later age at onset, being female, precipitating events, associated mood disturbance and no family history of schizophrenia.

2. Cognition and schizophrenia: history and theoretical models

Nowadays it is widely accepted that schizophrenia is caused by a cerebral dysfunction and cognitive deficits are among the common symptoms of schizophrenia. This does not diverge much from the first studies describing the

schizophrenia concept in the beginning of the last century. Especially, Bleuler who introduced the name "schizophrenia" in 1911 saw cognitive deficits as the fundamental phenomena in schizophrenia. After this publication however the neurocognitive research on schizophrenia felt into oblivion due to a lack of impressive results, to re-emerge in the last decades of the twentieth century. At present the most dominant heuristic model states that schizophrenia is caused by a neurobiological deficit, probably caused by genetic factors and detrimental events during early development. This causes psychopathology later in life because the affected brain areas mature later in life. In this model cognition is often viewed as an intermediate between neurobiological functioning and higher levels of functioning such as social functioning and self-awareness. Recent etiological theories, which incorporate neurobiological and cognitive functioning in schizophrenia, can be divided into three broad categories. The first category consists of those theories that view cognitive deficits as the core of the disease. Goldman-Rakic (1994) for example proposed that the fundamental impairment in schizophrenia is a defect in working memory, which is viewed as the ability to guide behavior by representational knowledge of the outside world. This is supposed to be caused by a dysfunction in the cortical processing networks by which the prefrontal cortex accesses and holds "on line" this representational knowledge through its connections with parietal and limbic areas. Hemsley (1994) proposes that the core deficit in schizophrenia is a weakening of the influence of stored memories on current input, caused by a disruption in the normal input tot the basal ganglia from the limbic system (Gray et al., 1991).

The second category of theories assumes that cognitive deficits and symptoms are both symptoms of the disease and are caused by the same neurobiological dysfunctions. Andreasen (1997) for example proposed that schizophrenia is caused by a deficit in the circuitry connecting the thalamus, frontal cortex and cerebellum, resulting in "cognitive dysmetria", which is characterized by an impairment in coordinating perception, encoding, retrieval and prioritization of experience and information, hence resulting in cognitive deficits and psychopathology.

Cornblatt (1999) suggests that a combination of several genes can cause neurobiological deficits, which eventually lead to schizophrenia. These

neurobiological deficits cause attention deficits on the one side and clinical symptoms on the other side. Both can cause social deficits.
The third category of theories views the syndrome as the results of different disease processes, causing cognitive deficits and symptoms independently. Murray (1987, 1992) for example proposed that two different processes can play a role, a distinct neurodevelopmental process, which has its origins in genetic deficits and early risk factors can cause premorbid symptoms, cognitive deficits and negative symptoms, while a high affective reactivity can induce positive symptoms in combination with stress-full circumstances.

3. Cognitive deficits in schizophrenia

Cognitive deficits are often found in schizophrenia. This paragraph gives an overview of the most important findings in several domains of cognitive functioning. The division in cognitive functions is only for clarity because this division is artificial and most tasks appeal to several functions at once. It is also important to realize that there is a distinction between the performance on a task and the underlying cognitive function it is supposed to measure. The former is called an indicator and the latter a construct.

Attention

It is very difficult to give a conclusive definition of attention. Globally speaking it is the mental power, which enables us to direct our mental capacity during some time, so we can perform well on a task. In the neuropsychological literature attention is often divided into four constructs. The first is sustained attention, the ability to maintain an information- processing task during a certain amount of time. The second, focused attention, aims at the ability to focus one attention on a particular stimulus, while other stimuli are ignored. The third, divided attention aims at the ability to divide ones attention between two or more different stimuli. The fourth is flexibility of attention, the ability to switch ones attention from one kind of stimulus to another.
More recent neurobiological research on the nature of attention shows that globally attention can be divided into two constructs, intensity and selectivity (Eling and van Zomeren, 1997). Intensity is the level of arousal or activity,

which enables a person to use its mental capacity for a task. By selectivity the attentional control functions are meant. Unfortunately, there are no proper indicators or tasks to measure these constructs selectively. This holds especially for intensity. Mostly correct signal detection or speed are taken as a global measure of intensity.

On signal-detection tasks performance there is no indication of impairment in sustained attention in schizophrenia. This would imply a time-on-task effect, which is not found. Vigilance, a state of readiness to detect and respond to certain small changes occurring at random time intervals in the environment (Nuechterlein et al., 1994) is most often assessed with the continuous performance paradigm, which involves tachistoscopic presentations of a quasi-random series of stimuli at a rapid fixed rate over 5-15 minutes with instructions to respond to a predestinated stimulus or sequence of stimuli (Nuechterlein et al., 1994). Variations with degraded visual images or in which one has to respond only if the designated target is preceded by a fixed target, exist. Schizophrenic patients as a group typically show impaired signal/noise discrimination on continuous performance tasks (Nuechterlein et al., 1991). Slowness in performing cognitive tests is a characteristic feature of schizophrenia, which has been well documented over the years (Nelson et al., 1990). Often used tasks are cancellation tasks, the Digit Symbol task from the WAIS, Trail Making Test part A and reaction time tasks. In a large meta-analysis of reaction time data from 40 studies (Schatz, 1997) a generalized slowing appears to be a significant aspect of information processing in schizophrenia.

The evidence for deficits in selectivity of attention in schizophrenia is less consistent. Often used indicators are the Stroop interference score and the Trail Making Test interference score and more complex reaction time tasks. In the most well known version of the Stroop paradigm, interference occurs when naming the print color of a word when the word itself has the name of another color. This is measured by the increased amount of time required to complete the task. According to Cohen and Serban-Schreiber (1992) schizophrenic patients show a clear interference effect. A number of studies did not replicate these findings (e.g. Taylor et al., 1996; Chen et al., 2001).

In a study with the Stroop and five other experimental inhibition tasks no differences were found between a group of first episode schizophrenic patients

and healthy controls (Broerse, 2002). The Trail Making Test is usually part of a larger test battery. The interference occurs when the subject must connect alternating letters and numbers. This is measured by the extra amount of time it takes to alternate instead of connecting only the numbers. In a large meta-analysis of cognitive functioning in schizophrenia (Heinrichs and Zakzanis, 1998), a large effect size is found on Trail Making Test interference, and only 2 out of 15 studies reviewed, did not find a significant effect. In a large meta-analysis on reaction time data (Schatz, 1997), there was an additional effect for problems with inhibition tasks next to a general slowing of information processing.

Memory

Memory is no unitary concept and can be divided in several systems and subsystems or processes (Schacter and Tulving, 1994). As for explicit memory, information first comes into primary memory or working memory (Baddeley and Hitch, 1974). This can be divided into three subsystems. Two short-term memory stores, the articulary loop and the visuospatial sketchpad, which hold information for maximum thirty seconds without interference, and the central executive, a more general cognitive function, which controls these systems. Information goes from short-term memory to long-term episodic memory by means of rehearsal or elaborate processing. Episodic memory enables people to encode and retrieve personal information, which is encoded in relation to spatial and temporal context. Three processes can be distinguished in manipulating episodic information: encoding, consolidation and explicit retrieval of information. The other long-term memory system is semantic memory, an organized amount of context-free knowledge, together with rules to manipulate this knowledge. Explicit retrieval processes can also play a role in the retrieval from semantic memory. In contrast to explicit memory, there is an implicit memory system, which deals with the uncontrolled or automatic use of several cognitive and motor processes, which are difficult to put into words.

The results of memory research in schizophrenia will be extensively described in chapter four. In sum, it may be stated that the memory deficits found in schizophrenia are explicit, verbal as well as visual and mostly concern active memory processes, such as encoding and retrieval processes in long-term memory systems.

Executive functions

Executive functions play a role in effortful cognitive processes. On a short time scale these functions are supposed to direct other cognitive functions, such as the allocation of attention, inhibition of automatic responses or switching of attention to different sources. On a larger time-scale they enable us to behave properly in novel situations in order to reach a certain goal. Goal formulating, planning, initiation and evaluation of performance then play an important role. The term executive functioning is often mixed up with "frontal functioning", because people with frontal lobe lesions often show deficits in executive functioning. Although the frontal lobes obviously play a role in executive functioning, this is not inclusive. Therefore the term executive function is preferred. The executive processes on a short time scale seem to resemble selective attention processes, and are measured with the same tasks such as Trailmaking Test interference and Stroop interference. Another often-used test for executive functioning is the Wisconsin Card Sorting Test (WCST; Heaton, 1993). In this test cards are used with figures of varying forms, colors and numbers. The subject has to sort the cards according to some unknown criterion (form, color or number) after each sort feedback is given whether the sort was correct or not. After a specified number of correct sorts, the sorting criterion is changed without notifying the subject. In most studies schizophrenic patients perform consistently worse than controls on this test (Heinrichs and Zakzanis, 1998, Johnson-Selfridge and Zalewski, 2001). The problem with this task is that it is rather difficult and calls upon many different functions such as memory, attention, learning, abstraction and of course executive functions; therefore it is difficult to say what causes problems in test performance.
It is rather difficult to test the executive processes on a larger time-scale because the highly structured and predictable nature of the test situation is the opposite of novel and unknown situations in which one has to call upon executive functions.

Intelligence

In general there are two theories defining intelligence. The multiple component theory states that intelligence is composed of several correlated functions. The other theory states that intelligence is one single factor called "g", for general

intelligence. The way in which both concepts of intelligence are assessed gives more insight into these constructs.

For both types of tests holds that the validity is reflected in their predictability for educational and occupational achievement. Almost all intelligence tests result in an IQ score with a mean of 100 and a standard deviation of 15.

The multiple component theory is operationalized in battery-like tests, which are made up out of several subtests. The idea behind it is that by computing the total results of all subtests, the specificity of each subtest disappears into the background. The intelligence score can be interpreted as the average efficiency of the total set of components. The most well known of these tests is the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1981).

One of the most often used tests to measure "g" is the Raven's Progressive Matrices (Raven et al., 1983). In this task one has to complete a visual pattern with one of several response alternatives, so that it becomes a coherent whole. Recent neuro-imaging research suggests that "g" derives from a specific frontal system, important for diverse forms of behavior by directing other cognitive processes (Duncan et al., 2000).

Another test often used in intelligence research is the National Adult Reading Task (NART; Nelson et al., 1991). This test is supposed to measure premorbid intelligence. The subject has to read out loud a list with different words with an irregular spelling; the ability to pronounce these words in the right way is supposed to be a robust indicator for premorbid functioning and has a high correlation with WAIS IQ in healthy individuals.

Schizophrenia patients as a group score lower on intelligence tests than would be predicted from family and environmental variables (Aylward et al., 1984). This is thought to result from two sources. Some studies have found evidence for a decline from premorbid performance after illness onset (Aylward et al., 1984; Gold, 1998). Some studies also found that schizophrenia patients had lower premorbid IQ as a child, than children who were unaffected (David et al., 1997; Kremen et al., 1998). However, Isohanni et al., (1999) found that schizophrenia could also be linked to very high intelligence.

4. Cognitive deficits in schizophrenia: is there a pattern?

The previous paragraph showed that a wide range of cognitive deficits is found in schizophrenia. A persistent question in the schizophrenia literature is whether this reflects a generalized or a specific cognitive deficit. The idea behind this question was that a specific deficit could point to the involvement of certain brain areas, which are supposed to play a role in the etiology of schizophrenia, whereas a more general deficit could point to more diffuse brain damage or even to non-specific factors, such as a lack of motivation or energy, or the interference of psychotic symptoms (Keefe, 1995). There is some support for a generalized deficit in the literature. Blanchard and Neale (1994) found a pattern of generalized dysfunction regardless of the method of analysis used to assess performance. But most recent studies support a specific cognitive deficit against a background of more general dysfunctioning (Censits et al., 1997; Saykin et al., 1991, 1994). In a large meta-analysis on 204 studies on cognitive differences between schizophrenia patients and controls, a general cognitive impairment was found with varying degrees of cognitive deficits for several domains. The largest impairment was documented for compound measures of global verbal memory, bilateral motor skills and performance IQ (Heinrichs and Zakzanis, 1998).

The problem with this kind of data is that it involves group comparisons while there are large inter-individual differences between patients. Not all patients, for example show cognitive deficits according to clinical norms (Palmer et al., 1997; Kremen et al., 2000). Large differences are also found between patients with cognitive deficits. Some patients only show a deficit in one domain of functioning, such as memory or executive deficits, while others show a range of cognitive deficits comprising all domains of functioning.

The question is how to cope with these inter-individual differences in cognitive research. In large group comparisons of schizophrenia patients versus controls a lot of information is lost due to the cognitive heterogeneity of the patients. Another way around is to search for different cognitive subgroups. Unfortunately this has not been very fruitful. Some researchers found small differences in psychopathology between cognitive subgroups (Heinrichs and Awad, 1993; McDermid and Heinrichs, 2002).

Studies on monozygotic twins discordant for schizophrenia, in which the ill twin almost always performed worse than the unaffected co-twin, however supported the idea that all patients have cognitive impairments instead of the existence of different subgroups. A dimensional approach, like in psychopathology research, may be the best way to analyze cognitive functioning in schizophrenia. Regarding etiology, one could suggest that one or more continuous neurobiological processes, which cause of variety of cognitive deficits, are affected to different degrees in schizophrenia.

5. Cognition and psychopathology

From the beginning of this century, attempts have been made to group patients into different subtypes of schizophrenia according to psychopathology (e.g. type I en II, Crow, 1980; positive and negative syndromes, Andreasen and Olson, 1982). In the last decade however a more dimensional approach to the study of schizophrenia has emerged. In this approach one tries to divide symptoms instead of patients into groups or dimensions. These dimensions are considered to be continuous and symptoms of several dimensions can co-occur in individuals (Andreasen et al., 1993). Factor analytic techniques were used to identify these dimensions in schizophrenia. Although there is some variability in these studies, consistencies emerge. In almost all studies a positive, a negative and a disorganization or cognitive component are found (Andreasen et al., 1994). Some studies also found an excitement and a depression-anxiety dimension (Kay and Sevy, 1990; Bell et al., 1992; Lindemayer et al., 1994, 1995). It has been suggested that these dimensions represent different underlying pathologies and therefore attempts have been made to find the different cognitive correlates of these psychopathology dimensions. This is described in chapter five. In sum, some correlations are found, but the results are not very consistent and the correlations, although statistically significant, are rather weak.

6. Cognition and functional outcome

Functional outcome in schizophrenia appears to be multidimensional, consisting of relatively independent domains such as interpersonal functioning, occupational functioning, independent functioning in community settings, performance on basic daily activities. A decline of functioning in one or more of these areas as compared with premorbid functioning is one of the diagnostic criteria for schizophrenia according to DSM-IV (APA, 1994). Social withdrawal or a problem to function properly in interpersonal contacts is often seen in schizophrenia. The majority of the patients show disabilities in social role performance fifteen years after illness onset (Wiersma et al., 2000). The onset of schizophrenia is also associated with a pronounced decline in employment (Mueser et al., 2001). Rates of competitive employment in schizophrenia tend to be low, with most estimates in the 10-20 percent range (Mueser et al., 2001). Although only a certain percentage of patients ends up staying in a psychiatric hospital or living in sheltered accommodation (14% in a large European study, Wiersma et al., 2000), a large percentage of the patients living in the community experience problems with independent functioning, performance of basic daily activities or leisure activities and therefore rely on community services. Quite a few studies have investigated the association between cognitive functioning and functional outcome, mostly with correlations or regression analyses (Green et al., 2000). Most studies use a wide range of cognitive variables and outcome measures, some studies even use laboratory assessment of social skills as outcome measures. These studies in general find highly significant correlations, but this could also be caused by the similarities between neuropsychological test conditions and laboratory social skill assessment. For clarity, only the results of studies assessing daily life functioning are reported.

Most cross-sectional studies find some significant correlations, but the explained variance is very low and due to the large number of measures there is always the possibility that the significant correlations are due to chance.

Fewer studies have investigated the predictive value of cognition on outcome, and only one study has used a first episode group to investigate the predictive value of cognitive measures at illness onset. The results of these studies are rather inconsistent and as yet no first episode study has been conducted in

which the predictive power of a broad range of cognitive variables has been investigated.

7. The multicenter study on schizophrenia

The studies described in chapter two, four and six of this thesis were based on data gathered with the multicenter study on neurobiological and neuropsychological predictors of functional status in first-onset schizophrenia: social disabilities, burden on the family, need for care and quality of life (ZonMw 940-33-015). This study was a collaboration of the university hospitals of Groningen, Amsterdam and Utrecht and focused on the predictive value of neuropsychological and neurobiological factors for functional outcome at two year follow-up in all first or second episode patients who were referred to the departments of psychiatry for treatment over a period of 1.5 years (1997 – 1998).

Diagnosis was based on structured interviews (SCAN; Wing et al., 1990; CASH; Andreasen et al., 1992). Exclusion criteria were severe mental retardation and a known systemic or neurological illness. A diagnosis of drugs or alcohol abuse or dependence was not an exclusion criterion, because this would exclude a substantial part of the first episode patients and leave a less representative cohort of this population.

Baseline measures at illness onset used for prediction were neurocognitive measures of attention, memory, executive functioning and intelligence and MRI-measurements. Data concerning obstetric complications, psychopathology, drugs or alcohol abuse or dependence, social functioning and burden of care were also gathered. Two years after inclusion follow-up data were collected concerning course of illness, psychopathology, social functioning, need for care and quality of life.

Initially one hundred and thirty eight patients were included. One hundred and eighteen completed the neurocognitive assessment and from this group one hundred and three also completed follow-up assessment.

8. Outline of this thesis

Chapter two presents a study on the characteristics of schizophrenia patients without clinically relevant cognitive deficits. These patients were studied in order to examine whether they represent an etiologically different subgroup, a general effect of disease severity or whether their cognitive deficits do not reach a clinical threshold due to a greater cognitive compensation capacity.
In ***chapter three*** the assumption that frontal impairment is a core deficit in schizophrenia is examined by means of both neuropsychological assessment and saccadic eye movements tasks in twenty-four recent onset patients. In addition, the relationship between saccadic and neuropsychological measures was studied.
In ***chapter four*** the question whether the memory impairments in schizophrenia should be understood as pure memory deficits or as the result of another underlying cognitive deficit is studied. One hundred eighteen recent onset patients from the multicenter study were compared with 45 controls on several memory tasks. The role of processing speed and central executive functions on memory performance was examined with regression analysis for all subjects and for patients separately.
Chapter five describes a study on the cognitive correlates of five symptom dimensions in a group of 50 recent onset psychotic patients. We were especially interested in the depression dimension, since it has not been studied extensively thus far. Both objective and subjective cognitive measured were used.
Chapter six presents a study on the predictive value of cognitive measures on course of illness and functional outcome in recent onset schizophrenia. One hundred and three first episode patients from the multicenter study participated in the follow-up assessment two years after inclusion. Differences in outcome between CI and CN patients were also analyzed.
In ***Chapter seven*** the results of all studies presented in this thesis are summarized, followed by some general conclusions concerning the nature and outcome of cognitive deficits in schizophrenia.

References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4thed. . American Psychiatric Association, Washington DC.

Andreasen, N.C., 1997. The role of the thalamus in schizophrenia. Can. J. Psychiatry 42, 27-33.

Andreasen, N.C., Carpenter, W.T.Jr., 1993. Diagnosis and classification of schizophrenia. schizophr. Bull. 19, 199-214.

Andreasen, N.C., Flaum, M., Arndt, S., 1992. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Arch. Gen. Psychiatry 49, 615-623.

Andreasen, N.C., Nopoulos, P., Schultz, S., Miller, D., Gupta, S., Swayze, V., Flaum, M., 1994. Positive and negative symptoms of schizophrenia: past, present, and future. Acta Psych. Scan. Suppl. 384, 51-59.

Andreasen, N.C., Olsen, S., 1982. Negative versus positive schizophrenia: definition and validation. Arch. Gen. Psychiatry 39, 789-794.

Aylward, E., Walker, E., Bettes, B., 1984. Intelligence in schizophrenia: a meta-analysis of the research. Schiz. Bull. 10, 430-459.

Baddeley, A.D. and Hitch, G., 1974. Working memory. In I.G.A. Bower (Ed.) The psychology of learning and motivation. Academic Press, New York, pp 47 – 90.

Belitsky, R, McGlashan, T.H., 1993. The manifestations of schizophrenia in late life: a dearth of data. Schiz. Bull. 19, 683-685.

Bell, M., Milstein, R., Beam Goulet, J., Lysaker, P., Cicchetti, D., 1992.The Positive and Negative Syndrome Scale and the Brief Psychiatric Rating Scale. Reliability, comparability, and predictive validity. J. Nerv. Ment. Dis. 180, 723-728.

Blanchard, J.J. and Neale, J.M., 1994. The neuropsychology of schizophrenia: generalized or differential deficit. Am. J. Psychiatry 151, 40-48.

Bleuler, E., 1911. Dementia Praecox oder Gruppe der Schizophrenien. In G. Aschaffenburg (Ed.) Handbuch der Psychiatrie. Deuticke, Leipzig /Wien.

Broerse, A., den Boer, J.A., submitted. Inhibition deficits in schizophrenia? A cognitive study.

Censits, D. M., Ragland, J. D., Gur, R. C., Gur, R. E., 1997. Neuropsychological evidence supporting a neurodevelopmental model of schizophrenia: a longitudinal study. Schizophr. Res. 24, 289-298.

Chen, E.Y.H., Wong, A.W.S., Chen, R.Y.L., Austin, G., 2001. Stroop interference and facilitation effects in first episode schizophrenic patients. Schizophr. Res. 48, 29-44.

Cohen, J.D., Servan-Schreiber, D., 1992. Context, cortex and dopamine: a connectionist approach to behavior and biology in schizophrenia. Psychol. Rev. 99, 45-77.

Cornblatt, B., Obuchowski, M., Roberts, S., Pollack, S., Erlenmeyer-Kimling, L., 1999. Cognitive and behavioral precursors of schizophrenia. Dev. Psychopatholol. 11, 487-508.

Crow, T.J., 1980. Positive and Negative schizophrenic symptoms and the role of Dopamine. Br. J. Psychiatry 137, 383-386.

David, A.S., Malmberg, A., Brandt, L., Allebeck, P., Lewis, G., 1997. IQ and risk for schizophrenia: a population-based cohort study. Psychol. Med. 27, 1311-1323.

Duncan, J., Seitz, R.J., Kolodny, J., Bor, D., Herzog, H., Ahmed, A., Newell, F.N., Emslie, H., 2000. A neural basis for general intelligence. Science 289, 457-460.

Eaton, W.W., Tien, A.Y. and Poeschla, B.D. 1995. Epidemiology of schizophrenia. In J.A. den Boer, H.G.M. Westenberg and H.M. van Praag (Eds.). Advances in the neurobiology of schizophrenia. John Wiley and sons, New York, pp 27-57.

Eling, P.A.T.M., van Zomeren, A.H. 1997. Aandacht. In B.G. Deelman, P.A.T.M. Eling, E.H.F. Haan, A. Jennekens-Schinkel, A.H. van Zomeren (Eds.). Klinische neuropsychologie. Boom, Amsterdam, pp 125-144.

Gold, J.M., 1998. Schizophrenia and intellectual decline. Am. J. Psychiatry 155, 1633-1634.

Goldman-Rakic, P. S., 1994. Working memory dysfunction in schizophrenia. J. Neuropsychiatry Clin. Neurosci. 6, 348-357.

Gray, J.A., Feldon, J., Rawlins, J.N., Hemsley, D.R., Smith, A.D., 1991. The neuropsychology of schizophrenia. Behav. Brain Sci., 14, 1-84.

Green, M. F., Kern, R. S., Braff, D. L., and Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schiz. Bull. 26, 119-136.

Harrison, G., Croudace, T., Mason, P., Galzebrook, C., Medley, I., 1996. Prediction the long-term outcome of schizophrenia. Psychol. Med. 26, 697-705.

Heaton, R.K, Chelune, G.J., Kay, K.K. Curtiss, G.,1993. Wisconsin Card Sorting Test manual: revised and expanded. Western Psychological Services, Los Angeles.

Hegarty, J.D., Baldessarini, R.J., Tohen, M., Waternaux, C. and Oepen, G., 1994. One hundred years of schizophrenia: a meta-analysis of the outcome literature. Am. J. Psychiatry 151, 1409 1416.

Hemsley, D.R., 1994. A cognitive model for schizophrenia and its possible neural basis. Acta. Psychiatr. Scand. Suppl. 384, 80-86.

Heinrichs, R.W., Awad, A.G., 1993., Neurocognitive subtypes of chronic schizophrenia. Schizophr. Res. 9, 49-58.

Heinrichs, R.W. & Zakzanis, K.K., 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12, 426-445.

Isohanni, I., Jarvelin, M.R., Jones, P., Jokelainen, J., Isohanni, M., 1999. Can excellent school performance be a precursor of schizophrenia? A 28-years follow-up in the Northern Finland 1966 birth cohort. Acta Psychiatr. Scand. 100, 17-26.

Johnson-Selfridge, M., Zalewski, C., 2001. Moderator variables of executive functioning I schizophrenia: meta-analytic findings. Schizophr. Bull. 27, 305-316.

Keefe, R. S., Roitman, S.E., Harvey, P.D., Blum, C.S., DuPre, R.L., Prieto, D.M., Davidson, M., Davis, K.L., 1995. A pen-and-paper human analogue of a monkey prefrontal cortex activation task: spatial working memory in patients with schizophrenia. Schizophr. Res. 17, 25-33.

Kremen, W.S., Buka, S.L., Seidman, L.J., Goldstein, J.M., Koren, D., Tsuang, M.T., 1998. IQ decline during childhood and adult psychotic symptoms in a community sample: a 19-year longitudinal study. Am. J. Psychiatry 155, 672-677.

Kremen, W.S., Seidman, L.J., Faraone, S.V., Toomey, R., Tsuang, M.T., 2000. The paradox of normal neuropsychological function in schizophrenia. J. Abnorm. Psychol. 109, 743-752.

Kay, S.R., Sevy, S., 1990. Pyramidical model of schizophrenia. Schizophr. Bull. 16,537-545.

Lindenmayer, J.P., Bernstein Hyman, R., Grochowski, S. A., 1994. A new five factor model of schizophrenia. Psychiatr. Q. 65, 299-322.

Lindenmayer, J.P., Grochowski, S., Hyman, R.B., 1995. Five factor model of schizophrenia: replication across samples. Schizophr. Res. 14, 229-234.

McDermid, S.A., Heinrichs, R.W., 2002. Schizophrenia and memory impairment: Murray, R.M., Lewis, S.W., 1987. Is schizophrenia a neurodevelopmental disorder? Br. J. Psychiatry 295, 681-682.

Mueser K.T., Salyers M.P., Mueser P.R., 2001. A prospective analysis of work in schizophrenia. Schizophr. Bull. 27, 281-296.

Murray, R.M., Jones, P., O'Callaghan, E., Takei, N., Sham, P., 1992. Genes, viruses and neurodevelopmental schizophrenia. J. Psychiatry Res. 26, 225-235.

Nelson, H.E., Pantelis, C., Carruthers, K., Speller, J., Baxendale, S. and Barnes, T.R., 1990. Cognitive functioning and symptomatology in chronic schizophrenia. Psychol. Med. 20, 357-365.

Nelson, H.E. and Willison, J.R., 1991. National Adult Reading Test (NART) Test manual. NFER Nelson Publishing Company, Windsor England.

Nuechterlein, K.H., 1991. Vigilance in schizophrenia and related disorders. In S.R. Steinhauer, J.H. Gruzelier and J. Zubin (Eds.), Handbook of schizophrenia. Vol. 5: Neuropsychology, psychophysiology and information processing. Elsevier, Amsterdam.

Nuechterlein, K.H., Buschbaum, M.S., Dawson, M.E., 1994. Neuropsychological vulnerability to schizophrenia. In A.S. David and J.C. Cutting (Eds.), The neuropsychology of schizophrenia. Lawrence Erlbaum Associates Ltd., Hove U.K.

Palmer, B.W., Heaton, R.K., Paulsen, J.S., Kuck, J., Braff, D., Harris, M.J., Zisook, S., Jeste, D.V., 1997. Is it possible to be schizophrenic yet neuropsychologically normal? Neuropsychology 11, 437-446.

Ram, R., Bromet, E.J., Eaton, W.W., Pato, C., Schwartz, J.E., 1992. The natural course of schizophrenia: a review of first admission studies. Schizophr. Bull. 10, 185-207.

Raven, J.C., Court, J.H. and Raven, J., 1983. Manual for Raven's Progressive Matrices and Vocabulary Scales. Section 1-7. Raven Ltd., Londen.

Saykin, A.J., Gur, R.C., Gur, R.E., Mozley, P.D., Mozley, L.H., Resnick, S.M., Kester, D.B. and Stafiniak, P., 1991. Neuropsychological function in schizophrenia. Selective impairment in memory and learning. Arch. Gen. Psychiatry 48, 618-624.

Saykin, A.J., Shtasel, D.L., Gur, R.E., Kester, D.B., Mozley, L.H., Stafiniak, P., Gur, R.C., 1994. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. Arch. Gen. Psychiatry, 51, 124-131.

Schacter, D.I. and Tulving, E., 1994. What are the memory systems of 1994. In D.I. Schacter and E. Tulving (Eds.). Memory systems 1994. MIT Press, Cambridge, pp. 1-38.

Schatz, J., 1998. Cognitive processing efficiency in schizophrenia: generalized vs domain specific deficits. Schizophr. Res. 30, 41-49.

Wechsler, D., 1981. Wechsler Adult Intelligence Scale-Revised. The Psychological Corporation, New York.

Wiersma, D., Wanderling, J., Dragomirecka, E., Ganev, K, Harrison, G., van der Heiden, W., Nienhuis, F.J., Walsh, D., 2000. Social disability in schizophrenia: its development and prediction over 15 years in incidence cohorts in six European centers. Psychol. Med. 30, 1155-1167.

Wing, J.K., Babor, T.F., Brugha, T.S., Burke, J., Cooper, J.E., Giel, R., Jablensky, A., Regier, D.A., Sartorius, N., 1990. SCAN Schedules for Clinical Assessment in Neuropsychiatry. Arch.Gen. Psychiatry 47, 589-593